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Signed Steph Hardy.

Dated 29 December 2003

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P01/7700 0.00-0305929.2

Patents Form 1/77

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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1.	Your reference	4-32910P1
2.	Patent application number *(The Patent Office will fill in this part)*	0305929.2 — 14 MAR 2003
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	07125487005
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
4.	Title of invention	Organic Compounds
5.	Name of your agent *(If you have one)*	
	[redacted]	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH 1800001

		Country	Priority application number *(if you know it)*	Date of filing (day/month/year)
6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number			

		Number of earlier application	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	37
Claim(s)	8
Abstract	1
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature: B. A. Yorke & Co.

Date: 14th March 2003

B.A. Yorke & Co.

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. S. Schnerr
020 8560 5847

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Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

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c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

d) *Once you have filled in the form you must remember to sign and date it.*

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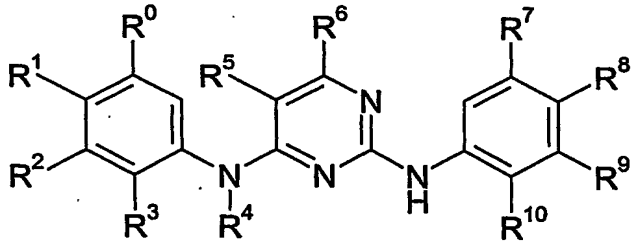
DUPLICATE

Organic Compounds

The present invention relates to novel pyrimidine derivatives, to processes for their production, their use as pharmaceuticals and to pharmaceutical compositions comprising them.

More particularly the present invention provides in a first aspect, a compound of formula I



(I)

wherein

each of R^0, R^1, R^2,and R^3 independently is hydrogen, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkinyl, C_3-C_8cycloalkyl, C_3-C_8cycloalkylC_1-C_8alkyl, C_5-C_{10}arylC_1-C_8alkyl, hydroxyC_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl, aminoC_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1, 2 or 3 hetero atoms selected from N, O and S, hydroxy, C_1-C_8alkoxy, hydroxyC_1-C_8alkoxy, C_1-C_8alkoxyC_1-C_8alkoxy, haloC_1-C_8alkoxy, unsubstituted or substituted C_5-C_{10}arylC_1-C_8alkoxy, unsubstituted or substituted heterocyclyloxy, or unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstitued or substituted amino, C_1-C_8alkylthio, C_1-C_8alkylsulfinyl, C_1-C_8alkylsulfonyl, C_5-C_{10}arylsulfonyl, halogen, carboxy, C_1-C_8alkoxycarbonyl, unsubstitued or substituted carbamoyl, unsubstitued or substituted sulfamoyl, cyano or nitro;

or R^0 and R^1, R^1 and R^2, and/or R^2 and R^3 form, together with the carbon atoms to which they are attached, a 5 or 6 membered carbocyclic or heterocyclic ring comprising 0, 1, 2 or 3 heteroatoms selected from N, O and S;

R^4 is hydrogen or C_1-C_8alkyl;

each of R^5 and R^6 independently is hydrogen, C_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl, haloC_1-C_8alkyl, C_1-C_8alkoxy, halogen, carboxy, C_1-C_8alkoxycarbonyl, unsubstitued or substituted carbamoyl, cyano, or nitro;

each of R^7, R^8, R^9, and R^{10} independently is C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkinyl, C_3-C_8cycloalkyl, C_3-C_8cycloalkylC_1-C_8alkyl, C_5-C_{10}arylC_1-C_8alkyl, hydroxyC_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl, aminoC_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1, 2 or 3

hetero atoms selected from N, O and S, hydroxy, C_1-C_8alkoxy, hydroxyC_1-C_8alkoxy, C_1-C_8alkoxyC_1-C_8alkoxy, haloC_1-C_8alkoxy, unsubstituted or substituted C_5-C_{10}arylC_1-C_8alkoxy, unsubstituted or substituted heterocyclyloxy, or unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstitued or substituted amino, C_1-C_8alkylthio, C_1-C_8alkylsulfinyl, C_1-C_8alkylsulfonyl, C_5-C_{10}arylsulfonyl, halogen, carboxy, C_1-C_8alkoxycarbonyl, unsubstitued or substituted carbamoyl, unsubstitued or substituted sulfamoyl, cyano or nitro;

or each of R^7, R^8 and R^9 independently is hydrogen;

or R^7 and R^8, R^8 and R^9, and/or R^9 and R^{10} form together with the carbon atoms to which they are attached, a 5 or 6 membered carbocyclic or heterocyclic ring comprising 0, 1, 2 or 3 heteroatoms selected from N, O and S;

and salts thereof.

The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated:

Where the plural form is used for compounds, salts, and the like, this is taken to mean also a single compound, salt, or the like.

Any asymmetric carbon atoms may be present in the (R)-, (S)- or (R,S)-configuration, preferably in the (R)- or (S)-configuration. The compounds may thus be present as mixtures of isomers or as pure isomers, preferably as enantiomer-pure diastereomers.

The invention relates also to possible tautomers of the compounds of formula I.

C_1-C_8alkyl denotes a an alkyl radical having from 1 up to 8, especially up to 4 carbon atoms, the radicals in question being either linear or branched with single or multiple branching; preferably, C_1-C_8alkyl is butyl, such as n-butyl, sec-butyl, isobutyl, tert-butyl, propyl, such as n-propyl or isopropyl, ethyl or methyl; especially methyl, propyl or tert-butyl.

C_2-C_8alkenyl denotes a an alkenyl radical having from 2 up to 8, especially up to 5 carbon atoms, the radicals in question being either linear or branched with single or multiple branching; preferably, C_2-C_8alkenyl is pentenyl, such as 3-methyl-2-buten-2-yl, butenyl, such as 1- or 2-butenyl or 2-buten-2-yl, propenyl, such as 1-propenyl or allyl, or vinyl.

C_2-C_8alkinyl denotes a an alkinyl radical having from 2 up to 8, especially up to 5 carbon atoms, the radicals in question being either linear or branched; preferably, C_2-C_8alkinyl is propinyl, such as 1-propinyl or propargyl, or acetylenyl.

C_3-C_8cycloalkyl denotes a cycloalkyl radical having from 3 up to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl, preferably cyclopropyl, cyclopentyl or cyclohexyl.

C_1-C_8alkoxy is especially methoxy, ethoxy, isopropyloxy, or tert-butoxy.

HydroxyC_1-C_8alkyl is especially hydroxymethyl, 2-hydroxyethyl or 2-hydroxy-2-propyl.

HydroxyC_1-C_8alkoxy is especially 2-hydroxyethoxy or 3-hydroxypropoxy.

C_1-C_8alkoxyC_1-C_8alkoxy is especially 2-methoxyethoxy.

C_1-C_8alkoxyC_1-C_8alkyl is especially methoxymethyl, 2-methoxyethyl or 2-ethoxyethyl.

Halogen is preferably fluorine, chlorine, bromine, or iodine, especially fluorine, chlorine, or bromine.

HaloC_1-C_8alkyl is preferably chloroC_1-C_8alkyl or fluoroC_1-C_8alkyl, especially trifluoromethyl or pentafluoroethyl.

HaloC_1-C_8alkoxy is preferably chloroC_1-C_8alkoxy or fluoroC_1-C_8alkoxy, especially trifluoromethoxy.

C_1-C_8alkoxycarbonyl is especially tert-butoxycarbonyl, iso-propoxycarbonyl, methoxycarbonyl or ethoxycarbonyl.

Unsubstitued or substituted carbamoyl is carbamoyl substituted by one or two substituents selected from hydrogen, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkinyl, C_3-C_8cycloalkyl, C_3-C_8cycloalkylC_1-C_8alkyl, C_5-C_{10}arylC_1-C_8alkyl, hydroxyC_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl, haloC_1-C_8alkyl, unsubstitued or substituted C_5-C_{10}aryl, or aminoC_1-C_8alkyl, or carbamoyl wherein the

substituents and the nitrogen atom of the carbamoyl group represent a 5 or 6 membered heterocyclyl further comprising 0, 1 or 2 hetero atoms selected from N, O and S; and is preferably carbamoyl, methylcarbamoyl, dimethylcarbamoyl, propylcarbamoyl, hydroxyethyl-methyl-carbamoyl, di(hydroxyethyl)carbamoyl, dimethylaminoethylcarbamoyl, or pyrrolidinocarbonyl, piperidinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, especially carbamoyl or dimethylcarbamoyl.

Unsubstitued or substituted sulfamoyl is sulfamoyl substituted by one or two substituents selected from hydrogen, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkinyl, C_3-C_8cycloalkyl, C_3-C_8cycloalkylC_1-C_8alkyl, C_5-C_{10}arylC_1-C_8alkyl, hydroxyC_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl, haloC_1-C_8alkyl, unsubstitued or substituted C_5-C_{10}aryl, or aminoC_1-C_8alkyl, or sulfamoyl wherein the substituents and the nitrogen atom of the sulfamoyl group represent a 5 or 6 membered heterocyclyl further comprising 0, 1 or 2 hetero atoms selected from N, O and S; and is preferably sulfamoyl, methylsulfamoyl, propylsulfamoyl, cyclopropylmethyl-sulfamoyl, 2,2,2-trifluoroethylsulfamoyl, dimethylaminoethylsulfamoyl, dimethylsulfamoyl, hydroxyethyl-methyl-sulfamoyl, di(hydroxyethyl)sulfamoyl, or pyrrolidinosulfonyl, piperidinosulfonyl, N-methylpiperazinosulfonyl or morpholinosulfonyl, especially sulfamoyl or methylsulfamoyl.

Unsubstitued or substituted amino is amino substituted by one or two substituents selected from hydrogen, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkinyl, C_3-C_8cycloalkyl, C_3-C_8cycloalkylC_1-C_8alkyl, C_5-C_{10}arylC_1-C_8alkyl, hydroxyC_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl, haloC_1-C_8alkyl, unsubstitued or substituted C_5-C_{10}aryl, aminoC_1-C_8alkyl, acyl, e.g. formyl, C_1-C_8alkylcarbonyl, C_5-C_{10}arylcarbonyl, C_1-C_8alkylsulfonyl or C_5-C_{10}arylsulfonyl, and is preferably amino, methylamino, dimethylamino, propylamino, benzylamino, hydroxyethyl-methyl-amino, di(hydroxyethyl)amino, dimethylaminoethylamino, acetylamino, acetyl-methyl-amino, benzoylamino, methylsulfonylamino or phenylsulfonylamino, especially amino or dimethylamino.

AminoC_1-C_8alkyl is especially aminoethyl, methylaminoethyl, dimethylaminoethyl or dimethylaminopropyl.

Unsubstitued or substituted C_5-C_{10}aryl is, for example, phenyl, indenyl, indanyl, naphthyl, or 1,2,3,4-tetrahydronaphthalenyl, optionally substituted by C_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl, haloC_1-C_8alkyl, hydroxy, C_1-C_8alkoxy, methylenedioxy, amino, substituted amino, halogen, carboxy, C_1-C_8alkoxycarbonyl, carbamoyl, sulfamoyl, cyano or nitro; preferably phenyl, tolyl,

trifluoromethylphenyl, methoxyphenyl, dimethoxyphenyl, methylenedioxyphenyl, chlorophenyl or bromophenyl, whereby the substituents may be in ortho, meta or para position, preferably meta or para.

C_5-C_{10}aryloxy is especially phenyoxy or methoxyphenoxy, e.g. p-methoxyphenoxy.

C_5-C_{10}arylC_1-C_8alkyl is especially benzyl or 2-phenylethyl.

C_5-C_{10}arylC_1-C_8alkoxy is especially bezyloxy or 2-phenylethoxy.

Unsubstitued or substituted 5 or 6 membered heterocyclyl comprising 1, 2 or 3 hetero atoms selected from N, O and S may be unsaturated, partially unsaturated or saturated, and further condensed to a benzo group or a 5 or 6 membered heterocyclyl group, and may be bound through a hetero or a carbon atom, and is, for example, pyrrolyl, indolyl, pyrrolidinyl, imidazolyl, benzimidazolyl, pyrazolyl, triazolyl, benzotriazolyl, tetrazolyl, pyridyl, quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, piperidyl, pyrimidinyl, pyrazinyl, piperazinyl, purinyl, tetrazinyl, oxazolyl, isoxalyl, morpholinyl, thiazolyl, benzothiazolyl, oxadiazolyl, and benzoxadiazolyl. Substituents considered are C_1-C_8alkyl, hydroxyC_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl, haloC_1-C_8alkyl, hydroxy, amino, substituted amino, C_1-C_8alkoxy, halogen, carboxy, C_1-C_8alkoxycarbonyl, carbamoyl, C_1-C_8alkylcarbamoyl, cyano, or oxo. 5 or 6 membered heterocyclyl preferably comprises 1 or 2 hetero atoms selected from N, O and S, and is especially indolyl, pyrrolidinyl, pyrrolidonyl, imidazolyl, N-methylimidazolyl, benzimidazolyl, S,S-dioxoisothiazolidinyl, piperidyl, 4-acetylaminopiperidyl, 4-methylcarbamoylpiperidyl, 4-piperidinopiperidyl, 4-cyanopiperidyl, piperazinyl, N-methylpiperazinyl, N-(2-hydroxyethyl)piperazinyl, morpholinyl, 1-aza-2,2-dioxo-2-thiacyclohexyl, or sulfolanyl.

In unsubstituted or substituted heterocyclyloxy, heterocyclyl has the meaning as defined above, and is especially N-methyl-4-piperidyloxy. In unsubstituted or substituted heterocyclylC_1-C_8alkoxy, heterocyclyl has the meaning as defined above, and is especially 2-pyrrolidinoethoxy, 3-morpholinopropoxy, 3-(N-methylpiperazino)propoxy or 2-(1-imidazolyl)ethoxy.

In a 5 or 6 membered carbocyclic or heterocyclic ring comprising 0, 1, 2 or 3 heteroatoms selected from N, O and S, and formed by two adjacent substituents together with the benzene ring, the ring may be further substituted, e.g. by C_1-C_8alkyl, C_1-C_8alkoxy, haloC_1-C_8alkyl,

hydroxy, amino, substituted amino, C_1-C_8alkoxy, halogen, carboxy, C_1-C_8alkoxycarbonyl, carbamoyl, cyano, or oxo. The two adjacent substituents forming such a ring are preferably propylene, butylene, 1-aza-2-propylidene, 3-aza-1-propylidene, 1,2-diaza-2-propylidene, 2,3-diaza-1-propylidene, 1-oxapropylene, 1-oxapropylidene, methylenedioxy, difluoromethylene-dioxy, 2-aza-1-oxopropylene, 2-aza-2-methyl-1-oxopropylene, 1-aza-2-oxopropylene, 2-aza-1,1-dioxo-1-thiapropylene or the corresponding butylene derivatives forming a 6 membered ring.

Salts are especially the pharmaceutically acceptable salts of compounds of formula I.

Such salts are formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of formula I with a basic nitrogen atom, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, 2-, 3- or 4-methylbenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

For isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed (where applicable in the form of pharmaceutical preparations), and these are therefore preferred.

In view of the close relationship between the novel compounds in free form and those in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, any reference to the free compounds

hereinbefore and hereinafter is to be understood as referring also to the corresponding salts, as appropriate and expedient.

The compounds of formula I have valuable pharmacological properties, as described hereinbefore and hereinafter.

In formula I the following significances are preferred independently, collectively or in any combination or sub-combination:

(a) each of R^0 or R^2 independently is hydrogen, C_1-C_8alkyl, e.g. methyl, ethyl or isopropyl, hydroxyC_1-C_8alkyl, e.g. hydroxyethyl or hydroxybutyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, unsubstituted or substituted C_5-C_{10}aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C_1-C_8alkoxy, e.g. methoxy, ethoxy or isopropoxy, haloC_1-C_8alkoxy, e.g. trifluoromethoxy, C_5-C_{10}aryloxy, e.g. phenoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, C_1-C_8alkylsulfonyl, e.g. methylsulfonyl, halogen, e.g. fluoro or chloro, unsubstituted or substituted carbamoyl, e.g. cyclohexylcarbamoyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl; preferably hydrogen, piperazino, N-methylpiperazino or 1-methyl-4-piperidyloxy, in particular hydrogen;

(b) R^1 is hydrogen, C_1-C_8alkyl, e.g. methyl, ethyl or isopropyl, hydroxyC_1-C_8alkyl, e.g. hydroxyethyl or hydroxybutyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, unsubstituted or substituted C_5-C_{10}aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C_1-C_8alkoxy, e.g. methoxy, ethoxy or isopropoxy, haloC_1-C_8alkoxy, e.g. trifluoromethoxy, C_5-C_{10}aryloxy, e.g. phenoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, C_1-C_8alkylsulfonyl, e.g. methylsulfonyl, halogen, e.g. fluoro or chloro, unsubstituted or substituted carbamoyl, e.g. cyclohexylcarbamoyl, piperidinocarbonyl,

piperazinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl; preferably hydrogen, piperazino, N-methylpiperazino, morpholino, 1-methyl-4-piperidinyloxy, 3-morpholinopropoxy or 2-morpholinoethoxy, in particular hydrogen;

(c) R^3 is hydrogen, C_1-C_8alkyl, e.g. methyl or ethyl, hydroxyC_1-C_8alkyl, e.g. hydroxyethyl or hydroxybutyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 heteroatoms selected from N, O and S, e.g. 2-pyrrolidonyl or S,S-dioxoisothiazolidinyl, C_1-C_8alkoxy, e.g. methoxy, substituted amino, e.g. acetylamino, acetyl-methyl-amino, benzoylamino, methylsulfonylamino or phenylsulfonyl-amino, C_1-C_8alkylsulfonyl, e.g. methylsulfonyl, C_5-C_{10}arylsulfonyl, e.g. phenylsulfonyl, halogen, e.g. fluoro or chloro, carboxy, substituted or unsubstituted carbamoyl, e.g. carbamoyl, methylcarbamoyl or dimethylcarbamoyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl, propylsulfamoyl, isopropylsulfamoyl, isobutylsulfamoyl, cyclopropylmethyl-sulfamoyl, 2,2,2-trifluoroethylsulfamoyl, dimethylsulfamoyl or morpholinosulfonyl; preferably sulfamoyl, methylsulfamoyl or propylsulfamoyl;

(d) each pair of adjacent substituents R^0 and R^1, or R^1 and R^2, or R^2 and R^3 are -CH_2-NH-CO-, -CH_2-CH_2-NH-CO-, -CH_2-CO-NH-, -CH_2-CH_2-CO-NH-, -CH_2-NH-SO_2-, -CH_2-CH_2-NH-SO_2-, -CH_2-SO_2-NH-, -CH_2-CH_2-SO_2-NH-, -CH_2-CH_2-SO_2-, -CH_2-CH_2-CH_2-SO_2-, -O-CH_2-O-, or -O-CF_2-O-, and such pairs wherein hydrogen in NH is replaced by C_1-C_8alkyl; preferably the pair of adjacent substituents R^0 and R^1, or R^1 and R^2 being -O-CH_2-O-, and the pair of adjacent substituents R^2 and R^3 being -CH_2-NH-CO- or -CH_2-NH-SO_2-.

(e) R^4 is hydrogen or C_1-C_8alkyl, e.g. methyl; preferably hydrogen;

(f) R^5 is hydrogen; C_1-C_8alkyl, e.g. methyl or ethyl, halogen, e.g. chloro or bromo, haloC_1-C_8alkyl, e.g. trifluoromethyl, cyano or nitro; preferably hydrogen, methyl, ethyl, chloro, bromo, trifluoromethyl or nitro; in particular chloro or bromo;

(g) R^6 is hydrogen;

(h) each of R^7 and R^9 independently is hydrogen, C_1-C_8alkyl, e.g. methyl, ethyl or isopropyl, hydroxyC_1-C_8alkyl, e.g. hydroxyethyl or hydroxybutyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, unsubstituted or substituted C_5-C_{10}aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C_1-C_8alkoxy, e.g. methoxy, ethoxy or isopropoxy, haloC_1-C_8alkoxy, e.g. trifluoromethoxy, C_5-C_{10}aryloxy, e.g. phenoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-

morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, C_1-C_8alkylsulfonyl, e.g. methylsulfonyl, halogen, e.g. fluoro or chloro, unsubstituted or substituted carbamoyl, e.g. cyclohexylcarbamoyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl; preferably hydrogen, methyl, isopropyl, trifluoromethyl, phenyl, methoxyphenyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, isopropoxy, phenoxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 2-(1-imidazolyl)ethoxy, dimethylamino, fluoro, morpholinocarbonyl, piperidinocarbonyl, piperazinocarbonyl or cyclohexylcarbamoyl;

(i) R^8 is hydrogen, C_1-C_8alkyl, e.g. methyl, ethyl or isopropyl, hydroxyC_1-C_8alkyl, e.g. hydroxyethyl or hydroxybutyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, C_5-C_{10}aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C_1-C_8alkoxy, e.g. methoxy, ethoxy or isopropoxy, haloC_1-C_8alkoxy, e.g. trifluoromethoxy, C_5-C_{10}aryloxy, e.g. phenoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino or dimethylamino, C_1-C_8alkylsulfonyl, e.g. methylsulfonyl, halogen, e.g. fluoro or chloro, unsubstituted or substituted carbamoyl, e.g. cyclohexylcarbamoyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl, cyano, or nitro; preferably hydrogen, methyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, trifluoromethoxy, phenoxy, 1-methyl-4-piperidyloxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 3-(N-methylpiperazino)-propoxy, methylamino, fluoro, chloro, sulfamoyl or nitro;

(j) R^{10} is C_1-C_8alkyl, e.g. methyl, ethyl or butyl, hydroxyC_1-C_8alkyl, e.g. hydroxyethyl or hydroxybutyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, C_1-C_8alkoxy, e.g. methoxy or ethoxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, e.g. 2-(1-imidazolyl)ethoxy, unsubstituted or substituted amino, e.g. methylamino or dimethylamino, halogen, e.g. fluoro or chloro; carboxy, carbamoyl, or unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl; preferably methyl, butyl, methoxy, ethoxy, 2-(1-imidazolyl)ethoxy, methylamino, dimethylamino or fluoro; and

(k) each pair of adjacent substituents R^7 and R^8, or R^8 and R^9 or R^9 and R^{10}, are –NH-CH=CH-, -CH=CH-NH-, –NH-N=CH-, –CH=N-NH-, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-O-$, -CH=CH-O-, $-O-CH_2-O-$, or $-O-CF_2-O-$; preferably the pair of adjacent substituents R^7 and R^8 or R^8 and R^9 being $-O-CH_2-O-$ or the pair of adjacent substituents R^9 and R^{10} being -NH-CH=CH-, -CH=N-NH-, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$ or $-O-CF_2-O-$.

More preferred are the following meanings, independently, collectively or in any combination or sub-combination:

(a') each of R^0 or R^2 independently is hydrogen, C_1-C_8alkyl, e.g. methyl, ethyl or isopropyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C_1-C_8alkoxy, e.g. methoxy, ethoxy or isopropoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, halogen, e.g. fluoro or chloro; preferably hydrogen, piperazino, N-methylpiperazino or 1-methyl-4-piperidyloxy, in particular hydrogen;

(b') R^1 is hydrogen, C_1-C_8alkyl, e.g. methyl, ethyl or isopropyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C_1-C_8alkoxy, e.g. methoxy, ethoxy or isopropoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, halogen, e.g. fluoro or chloro; preferably hydrogen, piperazino, N-methylpiperazino, morpholino, 1-methyl-4-piperidinyloxy, 3-morpholinopropoxy or 2-morpholinoethoxy, in particular hydrogen;

(c') R^3 is hydrogen, C_1-C_8alkyl, e.g. methyl or ethyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 heteroatoms selected from N, O and S, e.g. 2-pyrrolidonyl or S,S-dioxoisothiazolidinyl, C_1-C_8alkoxy, e.g. methoxy, substituted amino, e.g. acetylamino, acetyl-methyl-amino, benzoylamino, methylsulfonylamino or phenylsulfonylamino, C_1-C_8alkylsulfonyl, e.g. methylsulfonyl, C_5-C_{10}arylsulfonyl, e.g. phenylsulfonyl, halogen, e.g. fluoro or chloro, carboxy, substituted or

unsubstituted carbamoyl, e.g. carbamoyl, methylcarbamoyl or dimethylcarbamoyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl, propylsulfamoyl, isopropylsulfamoyl, isobutylsulfamoyl, cyclopropylmethyl-sulfamoyl, 2,2,2-trifluoroethylsulfamoyl, dimethylsulfamoyl or morpholinosulfonyl; preferably sulfamoyl, methylsulfamoyl or propylsulfamoyl;

(d') each pair of adjacent substituents R^0 and R^1, or R^1 and R^2, or R^2 and R^3 are $-CH_2-NH-CO-$, $-CH_2-NH-SO_2-$, $-CH_2-CH_2-SO_2-$, $-O-CH_2-O-$, or $-O-CF_2-O-$, and such pairs wherein hydrogen in NH is replaced by C_1-C_8alkyl; preferably the pair of adjacent substituents R^0 and R^1, or R^1 and R^2 being $-O-CH_2-O-$, and the pair of adjacent substituents R^2 and R^3 being $-CH_2-NH-CO-$ or $-CH_2-NH-SO_2-$.

(e') R^4 is hydrogen;

(f') R^5 is hydrogen, halogen, e.g. chloro or bromo, haloC_1-C_8alkyl, e.g. trifluoromethyl, or nitro; preferably hydrogen, chloro, bromo, trifluoromethyl or nitro; in particular chloro or bromo;

(g') R^6 is hydrogen;

(h') each of R^7 and R^9 independently is hydrogen, C_1-C_8alkyl, e.g. methyl, ethyl or isopropyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, unsubstituted or substituted C_5-C_{10}aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C_1-C_8alkoxy, e.g. methoxy, ethoxy or isopropoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, halogen, e.g. fluoro or chloro, unsubstituted or substituted carbamoyl, e.g. cyclohexylcarbamoyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl; preferably hydrogen, methyl, isopropyl, trifluoromethyl, phenyl, o-, m- or p-methoxyphenyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, isopropoxy, phenoxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 2-(1-imidazolyl)ethoxy, dimethylamino, fluoro, morpholinocarbonyl, piperidinocarbonyl, piperazinocarbonyl or cyclohexylcarbamoyl;

(i') R^8 is hydrogen, C_1-C_8alkyl, e.g. methyl, ethyl or isopropyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, C_5-C_{10}aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C_1-C_8alkoxy, e.g. methoxy, ethoxy or

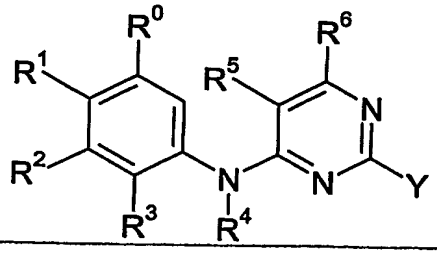
isopropoxy, haloC_1-C_8alkoxy, e.g. trifluoromethoxy, C_5-C_{10}aryloxy, e.g. phenoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino or dimethylamino, halogen, e.g. fluoro or chloro, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl, or nitro; preferably hydrogen, methyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, trifluoromethoxy, phenoxy, 1-methyl-4-piperidyloxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 3-(N-methylpiperazino)-propoxy, methylamino, fluoro, chloro, sulfamoyl or nitro;

(j') R^{10} is C_1-C_8alkyl, e.g. methyl, ethyl or butyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, C_1-C_8alkoxy, e.g. methoxy or ethoxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, e.g. 2-(1-imidazolyl)ethoxy, unsubstituted or substituted amino, e.g. methylamino or dimethylamino, halogen, e.g. fluoro or chloro; preferably methyl, butyl, methoxy, ethoxy, 2-(1-imidazolyl)ethoxy, methylamino, dimethylamino or fluoro; and

(k') each pair of adjacent substituents R^7 and R^8, or R^8 and R^9 or R^9 and R^{10}, are –NH-CH=CH-, -CH=CH-NH-, –NH-N=CH-, –CH=N-NH-, -CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2-, -O-CH_2-O-, or -O-CF_2-O-; preferably the pair of adjacent substituents R^7 and R^8 or R^8 and R^9 being -O-CH_2-O- or the pair of adjacent substituents R^9 and R^{10} being -NH-CH=CH-, -CH=N-NH-, -CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2- or -O-CF_2-O-.

Most preferred as compounds of the formula I are those wherein the substituents have the meaning given in the Examples.

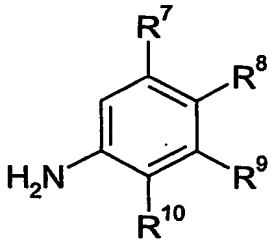
The present invention also provides a process for the production of a compound of formula I, comprising reacting a compound of formula II



(II)

wherein R^0, R^1, R^2, R^3, R^4, R^5, and R^6 are as defined above, and Y is a leaving group, preferably halogen such as bromide, iodine, or in particular chloride;

with a compound of formula III



(III)

wherein R^7, R^8, R^9 and R^{10} are as defined above;

and, if desired, converting a compound of formula I, wherein the substituents have the meaning as defined above, into another compound of formula I as defined;

and recovering the resulting compound of formula I in free from or as a salt, and, when required, converting the compound of formula I obtained in free form into the desired salt, or an obtained salt into the free form.

The reaction can be carried out in a manner known per se, the reaction conditions being dependent especially on the reactivity of the leaving group Y and the reactivity of the amino group in the aniline of formula III, usually in the presence of a suitable solvent or diluent or of a mixture thereof and, if necessary, in the presence of an acid or a base, with cooling or, preferably, with heating, for example in a temperature range from approximately -30°C to approximately +150°C, especially approximately from 0°C to +100°C, preferably from room temperature (approx. +20 °C) to +80 °C, in an open or closed reaction vessel and/or in the atmosphere of an inert gas, for example nitrogen.

If one or more other functional groups, for example carboxy, hydroxy or amino, are or need to be protected in a compound of formula II or III, because they should not take part in the reaction, these are such groups as are usually used in the synthesis of peptide compounds, cephalosporins and penicillins, as well as nucleic acid derivatives and sugars.

The protecting groups may already be present in precursors and should protect the functional groups concerned against unwanted secondary reactions, such as substitution reaction or solvolysis. It is a characteristic of protecting groups that they lend themselves readily, i.e.

without undesired secondary reactions, to removal, typically by solvolysis, reduction, photolysis or also by enzyme activity, for example under conditions analogous to physiological conditions, and that they are not present in the end-products. The specialist knows, or can easily establish, which protecting groups are suitable with the reactions mentioned hereinabove.

Salts of a compound of formula I with a salt-forming group may be prepared in a manner known per se. Acid addition salts of compounds of formula I may thus be obtained by treatment with an acid or with a suitable anion exchange reagent.

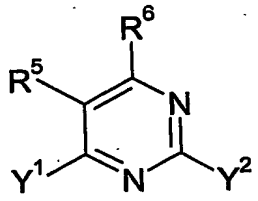
Salts can usually be converted to compounds in free form, e.g. by treating with suitable basic agents, for example with alkali metal carbonates, alkali metal hydrogencarbonates, or alkali metal hydroxides, typically potassium carbonate or sodium hydroxide.

Stereoisomeric mixtures, e.g. mixtures of diastereomers, can be separated into their corresponding isomers in a manner known per se by means of suitable separation methods. Diastereomeric mixtures for example may be separated into their individual diastereomers by means of fractionated crystallization, chromatography, solvent distribution, and similar procedures. This separation may take place either at the level of a starting compound or in a compound of formula I itself. Enantiomers may be separated through the formation of diastereomeric salts, for example by salt formation with an enantiomer-pure chiral acid, or by means of chromatography, for example by HPLC, using chromatographic substrates with chiral ligands.

It should be emphasized that reactions analogous to the conversions mentioned in this chapter may also take place at the level of appropriate intermediates.

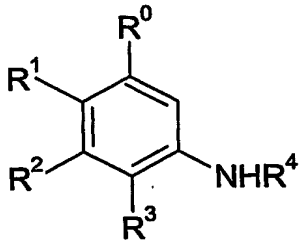
The compounds of formula I, including their salts, are also obtainable in the form of hydrates, or their crystals can include for example the solvent used for crystallization (present as solvates).

The compound of formula II used as starting materials may be obtained by reacting a compound of formula IV



(IV)

with a compound of formula V



(V)

wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined above, and Y^1 and Y^2 are identical or different leaving groups as defined above for Y. The reaction conditions are those mentioned above for the reaction of a compound of formula II with a compound of formula III.

The compounds of formula IV and V are known or may be produced in accordance with known procedures.

The compounds of formula I and their pharmaceutically acceptable salts exhibit valuable pharmacological properties when tested in vitro in cell-free kinase assays and in cellular assays, and are therefore useful as pharmaceuticals. In particular, the compounds of the invention are inhibitors of Focal Adhesion Kinase, and are useful as pharmaceuticals to treat conditions caused by a malfunction of signal cascades connected with Focal Adhesion Kinase, in particular tumors as described hereinbelow.

Focal Adhesion Kinase (FAK) is a key enzyme in the integrin-mediated outside-in signal cascade (D. Schlaepfer et al., Prog Biophys Mol Biol 1999, 71, 435-478). Interaction between cells and extracellular matrix (ECM) proteins is transduced as intracellular signals important for growth, survival and migration through cell surface receptors, integrins. FAK plays an essential role in these integrin-mediated outside-in signal cascades. The trigger in the signal transduction cascade is the autophosphorylation of Y397. Phosphorylated Y397 is a SH2 docking site for Src family tyrosine kinases. The bound c-Src kinase phosphorylates other tyrosine residues in FAK. Among them, phsophorylated Y925 becomes a binding site for the SH2 site of Grb2 small

adaptor protein. This direct binding of Grb2 to FAK is one of the key steps for the activation of down stream targets such as the Ras-ERK2/MAP kinase cascade.

The inhibition of endogenous FAK signalling results in reduced motility and in some cases induces cell death. On the other hand, enhancing FAK signalling by exogenous expression increases cell motility and transmitting a cell survival signal from ECM. In addition FAK is overexpressed in invasive and metastatic epithelial, mesenchymal, thyroid and prostate cancers. Consequently, an inhibitor of FAK is likely to be a drug for anti-tumor growth and metastasis. The compounds of the invention are thus indicated, for example, to prevent and/or treat a vertebrate and more particularly a mammal, affected by a neoplastic disease, in particular breast tumor, cancer of the bowel (colon and rectum), stomach cancer and cancer of the ovary and prostate, non-small cell lung cancer, small cell lung cancer, cancer of liver, melanoma, bladder tumor and cancer of head and neck.

The relation between FAK inhibition and immuno-system is described e.g. in G.A. van Seventer et al., Eur. J. Immunol. 2001, 31, 1417-1427. Therefore, the compounds of the invention are, for example, useful to prevent and/or treat a vertebrate and more particularly a mammal, affected by immune system disorders, diseases or disorders mediated by T lymphocytes, B lymphocytes, mast cells and/or eosinophils e.g. acute or chronic rejection of organ or tissue allo- or xenografts, atherosclerosis, vascular occlusion due to vascular injury such as angioplasty, restenosis, hypertension, heart failure, chronic obstructive pulmonary disease, CNS disease such as Alzheimer disease or amyotrophic lateral sclerosis, cancer, infectious disease such as AIDS, septic shock or adult respiratory distress syndrome, ischemia/reperfusion injury e.g. myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, or traumatic shock. The agent of the invention are also useful in the treatment and/or prevention of acute or chronic inflammatory diseases or disorders or autoimmune diseases e.g. rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, diabetes (type I and II) and the disorders associated with therewith, respiratory diseases such as asthma or inflammatory liver injury, inflammatory glomerular injury, cutaneous manifestations of immunologically-mediated disorders or illnesses, inflammatory and hyperproliferative skin diseases (such as psoriasis, atopic dermatitis, allergic contact dermatitis, irritant contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis), inflammatory eye diseases, e.g. Sjoegren's syndrome, keratoconjunctivitis or uveitis, inflammatory bowel disease, Crohn's disease or ulcerative colitis.

Compounds of the invention are active in a FAK assay system as described in the Examples, and show an inhibition IC50 in the range of 1 nM to 100 nM. Particularly active are the compounds Example No. 3-12 and No. 3-17 described hereinbelow showing IC50 vales in the range of 1 to 5 nM.

Some of the compounds of the invention exhibit also ZAP-70 (zeta chain-associated protein of 70 kD) protein tyrosine kinase inhibiting activity. ZAP-70 protein tyrosine kinase interaction of the agents of the invention may be demonstrated by their ability to prevent phosphorylation of e.g. LAT-11 (linker for activation of T cell) by human ZAP-70 protein tyrosine kinase in aqueous solution, as described in the Examples. The compounds of the invention are thus also indicated for the prevention or treatment of disorders or diseases where ZAP-70 inhibition inhibition play a role.
Compounds of the invention are active in a ZAP-70 assay system as described in the Examples, and show an inhibition IC50 in the range of 1 μM to 10 μM, e.g. the compounds Example No. 2 and No. 3-2 described hereinbelow.

For the above uses in the treatment of neoplastic diseases and immune system disorders the required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.1 to about 100 mg/kg body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5 mg to about 2000 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form.

The compounds of the invention may be administered by any conventional route, in particular parenterally, for example in the form of injectable solutions or suspensions, enterally, preferably orally, for example in the form of tablets or capsules, topically, e.g. in the form of lotions, gels, ointments or creams, or in a nasal or a suppository form. Pharmaceutical compositions comprising an compound of the invention in association with at least one pharmaceutical acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent. Unit dosage forms for oral administration contain, for example, from about 0.1 mg to about 500 mg of active substance. Topical administration is e.g. to the skin. A further form of topical administration is to the eye.

The pharmaceutical compositions of the present invention are prepared in a manner known per se, for example by means of conventional mixing, granulating, coating, dissolving or lyophilizing processes.

Preference is given to the use of solutions of the active ingredient, and also suspensions or dispersions, especially isotonic aqueous solutions, dispersions or suspensions which, for example in the case of lyophilized compositions comprising the active ingredient alone or together with a carrier, for example mannitol, can be made up before use. The pharmaceutical compositions may be sterilized and/or may comprise excipients, for example preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating osmotic pressure and/or buffers and are prepared in a manner known per se, for example by means of conventional dissolving and lyophilizing processes. The said solutions or suspensions may comprise viscosity-increasing agents, typically sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone, or gelatins, or also solubilizers, e.g. Tween 80® (polyoxyethylene(20)sorbitan mono-oleate).

Suspensions in oil comprise as the oil component the vegetable, synthetic, or semi-synthetic oils customary for injection purposes. In respect of such, special mention may be made of liquid fatty acid esters that contain as the acid component a long-chained fatty acid having from 8 to 22, especially from 12 to 22, carbon atoms, for example lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brassidic acid or linoleic acid, if desired with the addition of antioxidants, for example vitamin E, β-carotene or 3,5-di-tert-butyl-4-hydroxytoluene. The alcohol component of these fatty acid esters has a maximum of 6 carbon atoms and is a monovalent or polyvalent, for example a mono-, di- or trivalent, alcohol, for example methanol, ethanol, propanol, butanol or pentanol or the isomers thereof, but especially glycol and glycerol. As fatty acid esters, therefore, the following are mentioned: ethyl oleate, isopropyl myristate, isopropyl palmitate, "Labrafil M 2375" (polyoxyethylene glycerol), "Labrafil M 1944 CS" (unsaturated polyglycolized glycerides prepared by alcoholysis of apricot kernel oil and consisting of glycerides and polyethylene glycol ester), "Labrasol" (saturated polyglycolized glycerides prepared by alcoholysis of TCM and consisting of glycerides and polyethylene glycol ester; all available from Gattefossé, France), and/or "Miglyol 812" (triglyceride of saturated fatty acids of chain length C_8 to C_{12} from Hüls AG,

Germany), but especially vegetable oils such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and more especially groundnut oil.

The manufacture of injectable preparations is usually carried out under sterile conditions, as is the filling, for example, into ampoules or vials, and the sealing of the containers.

Pharmaceutical compositions for oral administration can be obtained, for example, by combining the active ingredient with one or more solid carriers, if desired granulating a resulting mixture, and processing the mixture or granules, if desired or necessary, by the inclusion of additional excipients, to form tablets or tablet cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations, and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate. Additional excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

Tablet cores can be provided with suitable, optionally enteric, coatings through the use of, inter alia, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or tablet coatings, for example for identification purposes or to indicate different doses of active ingredient.

Pharmaceutical compositions for oral administration also include hard capsules consisting of gelatin, and also soft, sealed capsules consisting of gelatin and a plasticizer, such as glycerol or sorbitol. The hard capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders, and/or glidants, such as talc or magnesium stearate, and optionally stabilizers. In soft capsules, the active ingredient is

preferably dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols or fatty acid esters of ethylene or propylene glycol, to which stabilizers and detergents, for example of the polyoxyethylene sorbitan fatty acid ester type, may also be added.

Pharmaceutical compositions suitable for rectal administration are, for example, suppositories that consist of a combination of the active ingredient and a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

For parenteral administration, aqueous solutions of an active ingredient in water-soluble form, for example of a water-soluble salt, or aqueous injection suspensions that contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if desired, stabilizers, are especially suitable. The active ingredient, optionally together with excipients, can also be in the form of a lyophilizate and can be made into a solution before parenteral administration by the addition of suitable solvents.

Solutions such as are used, for example, for parenteral administration can also be employed as infusion solutions.

Preferred preservatives are, for example, antioxidants, such as ascorbic acid, or microbicides, such as sorbic acid or benzoic acid.

The compounds of the invention may be administered as the sole active ingredient or together with other drugs useful against neoplastic diseases or useful in immunomodulating regimens. For example, the agents of the invention may be used in accordance with the invention in combination with pharmaceutical compositions effective in various diseases as described above, e.g. with cyclophosphamide, 5-fluorouracil, fludarabine, gemcitabine, cisplatinum, carboplatin, vincristine, vinblastine, etoposide, irinotecan, paclitaxel, docetaxel, rituxan, doxorubicine, gefitinib, or imatinib; or also with cyclosporins, rapamycins, ascomycins or their immunosuppressive analogs, e.g. cyclosporin A, cyclosporin G, FK-506, sirolimus or everolimus, corticosteroids, e.g. prednisone, cyclophosphamide, azathioprene, methotrexate, gold salts, sulfasalazine, antimalarials, brequinar, leflunomide, mizoribine, mycophenolic acid, mycophenolate, mofetil, 15-deoxyspergualine, immuno-suppressive monoclonal antibodies, e.g.

monoclonal antibodies to leukocyte receptors, e.g. MHC, CD2, CD3, CD4, CD7, CD25, CD28, CD40, CD45, CD58, CD80, CD86, CD152, CD137, CD154, ICOS, LFA-1, VLA-4 or their ligands, or other immunomodulatory compounds, e.g. CTLA4Ig.

In accordance with the foregoing, the present invention also provides:

(1) A compound of the invention for use as a pharmaceutical;
(2) a compound of the invention for use as a FAK inhibitor and/or ZAP-70 inhibitor, for example for use in any of the particular indications hereinbefore set forth;
(3) a pharmaceutical composition, e.g. for use in any of the indications herein before set forth, comprising a compound of the invention as active ingredient together with one or more pharmaceutically acceptable diluents or carriers;
(4) a method for the treatment of any particular indication set forth hereinbefore in a subject in need thereof which comprises administering an effective amount of a compound of the invention or a pharmaceutical composition comprising same;
(5) the use of a compound of the invention for the manufacture of a medicament for the treatment or prevention of a disease or condition in which FAK and/or ZAP-70 activation plays a role or is implicated;
(6) a method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of a compound of the invention and one or more further drug substances, said further drug substance being useful in any of the particular indications set forth hereinbefore;
(7) a combination comprising a therapeutically effective amount of a compound of the invention and one or more further drug substances, said further drug substance being useful in any of the particular indications set forth hereinbefore.

The following Examples serve to illustrate the invention without limiting the invention in its scope.

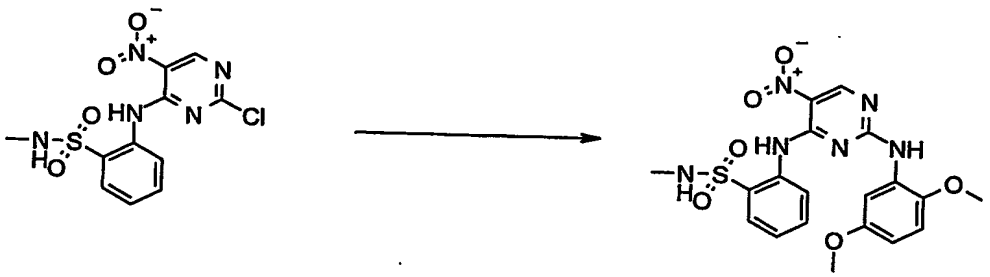
Examples

Abbreviations

ATP = adenosine 5'-triphosphate, BSA = bovine serum albumin, DIAD = diisopropyl azodicarboxylate, DIPCDI = N,N'-diisopropylcarbodiimid, DMAP = 4-dimethylaminopyridine,

DTT = 1,4-dithio-D,L-threitol, EDTA = ethylene diamine tetraacetic acid, Eu-PT66 = LANCE™ europium-W1024-labelled anti-phosphotyrosine antibody (Perkin Elmer), FAK = Focal Adhesion Kinase, FRET = fluorescence resonance energy transfer, HEPES = N-2-hydroxyethyl-piperazine-N'-2-ethanesulfonic acid, HOAt = 1-hydroxy-7-azabenzotriazole, RT-PCR = reverse transcription polymerase chain reaction, TBTU = O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyl-ammonium tetrafluoroborate, SA-(SL)APC = Streptavidin conjugated to SuperLight™ allophycocyanin (Perkin Elmer)

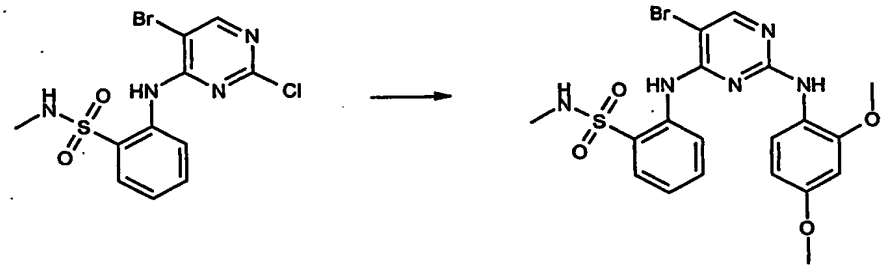
Example 1: 2-[2-(2,5-Dimethoxy-phenylamino)-5-nitro-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide



To a solution of 2-(2-chloro-5-nitro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide (100 mg, 0.29 mmol) in EtOH (3 mL), 2,5-dimethoxyaniline (49 mg, 0.32 mmol) is added at room temperature. The mixture is heated at 78°C for 5 h. The solvent is evaporated, and the mixture is purified by reverse phase HPLC to give the title product in.
Rf = 0.47 (n-hexane : ethyl acetate = 1:1). ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 2.36 (d, 3H), 3.57 (s, 3H), 3.73 (s, 3H), 6.72 (d, 1H), 6.99 (d, 1H), 7.17 (s, 1H), 7.35 (t, 1H), 7.4-7.6 (m, 1H), 7.63 (d, 1H), 7.81 (d, 1H), 8.0-8.2 (m, 1H), 9.13 (s, 1H), 9.41 (br.s, 1H), 11.0 (s, 1H).

Preparation of 2-(2-chloro-5-nitro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide:
2,4-Dichloro-5-nitro-pyrimidine (1.94 g, 10 mmol) and 2-amino-N-methyl-benzenesulfonamide (1.86 g, 10 mmol) are dissolved in $CHCl_3$ (30 mL). The reaction mixture is heated at 61°C for 2 h. The solvent is evaporated and the residue is washed with ether to give the title product.
Rf = 0.5 (n-hexane : ethyl acetate = 1:1). ^{1}H-NMR (400MHz, $CDCl_3$), δ (ppm): 2.67 (d, 3H), 4.6-4.7 (m, 2H), 7.41 (t, 1H), 7.7 (t, 1H), 8.04 (d, 1H), 8.15 (d, 1H), 9.21 (s, 1H), 11.2 (s, 1H).

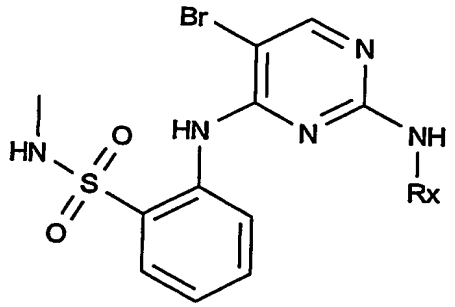
~~Example 2: 2-[5-Bromo-2-(2,4-dimethoxy-phenylamino)-pyrimidin-4-ylamino]-N-methyl-~~ benzenesulfonamide

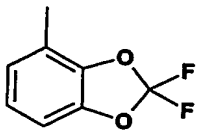
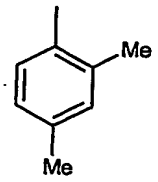
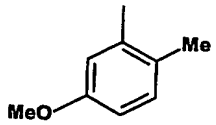
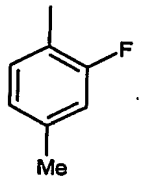
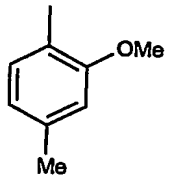
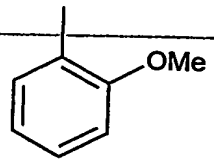


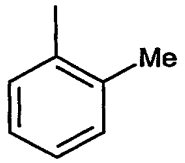
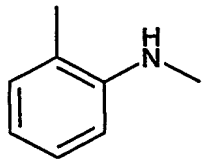
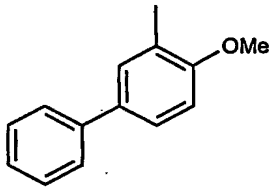
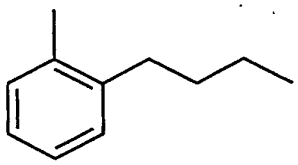
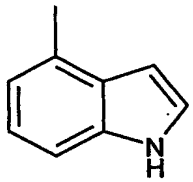
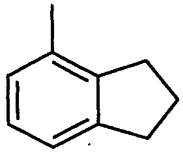
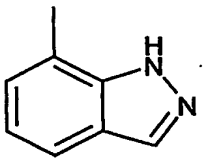
To a solution of 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide (300 mg, 0.79 mmol), 2,4-dimethoxyaniline (181.5 mg, 1.18 mmol) in ethanol (3 mL), 1 N hydrochloric acid (0.03 mL) is added and stirred under reflux condition for 5 hours. The reaction mixture is cooled to room temperature, poured into water and extracted twice with ethyl acetate. The organic layer is successively washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane : ethyl acetate = 5:1 to 1:1) to afford the title compound.
^{1}H-NMR ($CDCl_3$), δ (ppm): 8.95 (s, 1H), 8.44 (d, 1H), 8.20 (s, 1H), 7.98 (dd, 1H), 7.58 (dt, 1H), 7.22-7.32 (m, 1H), 6.51 (d, 1H), 6.40 (d, 1H), 4.56-4.48 (m, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 2.64 (d, 3H). Rf (n-hexane : ethyl acetate = 1:1): 0.31.

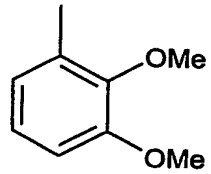
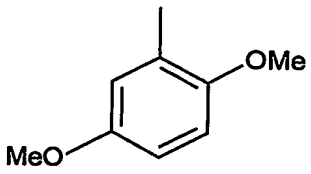
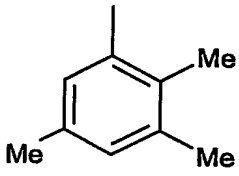
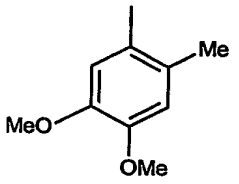
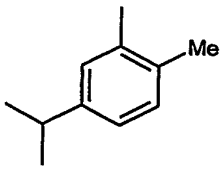
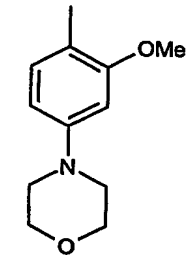
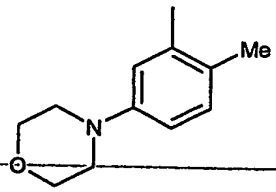
Preparation of 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide
A solution of 5-bromo-2,4-dichloropyrimidine (684 mg, 3.0 mmol) and 2-amino-N-methyl-benzenesulfonamide (559 mg, 3.0 mmol) in N,N-dimethylformamide (10 mL) containing potassium carbonate (830 mg, 6.0 mmol) is stirred at room temperature for 23 hours. Saturated aqueous ammonium chloride is added and the mixture is poured into water and extracted twice with ethyl acetate. The organic layer is washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane - ethyl acetate gradient) to afford the title compound as a slightly yellow solid.
^{1}H-NMR ($CDCl_3$), δ (ppm): 2.67 (d, 3H), 4.79 (q, 1H), 7.26 (s, 1H), 7.29 (ddd, 1H), 7.66 (ddd, 1H), 7.95 (dd, 1H), 8.37 (s, 1H), 8.48 (d, 1H), 9.52 (s, 1H). Rf (n-hexane : ethyl acetate = 10:3): 0.33.

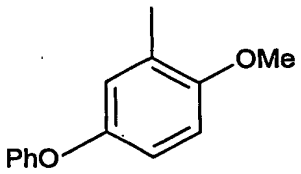
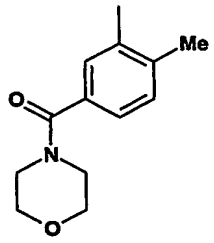
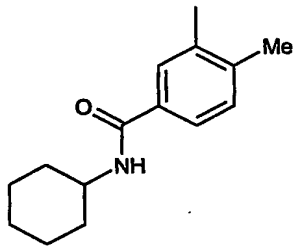
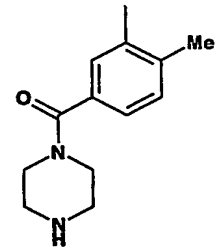
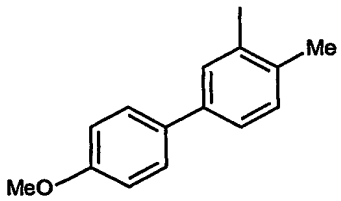
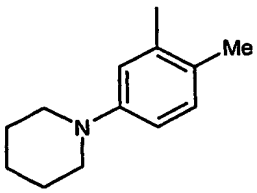
Example 3:
The following 2-[5-bromo-2-(subst.phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzene-sulfonamides were prepared from 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide and the corresponding aniline following the procedure of Example 2:

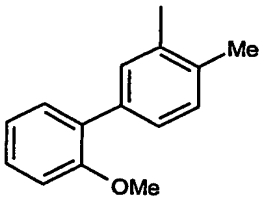
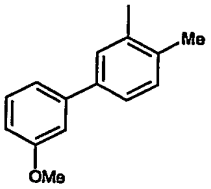
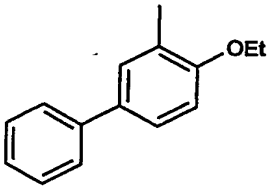
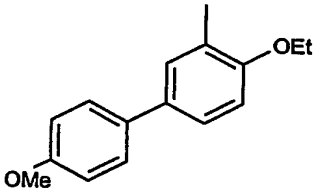
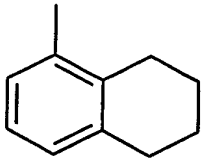


Expl No.	Rx	Rf (solvent)	NMR (400MHz) in $CDCl_3$, δ (ppm)
3-1		0.48 (*n*-hexane: AcOEt=1:1)	2.64(d, 3H),4.48-4.40(m, 1H), 6.78(d,1H), 6.87(bs, 1H),6.99(dd, 1H),6.82(s, 1H),7.54(dt, 1H), 7.79(d, 1H),7.97(dd, 1H), 8.28(s, 1H), 8.32(dd, 1H), 9.07(s, 1H)
3-2		0.58 (*n*-hexane: AcOEt=1:1)	2.25(s, 3H),2.33(s, 3H),2.63(d, 3H),4.53-4.45(m, 1H),6.61(bs, 1H),6.99(dd, 1H), 7.04(s, 1H),7.18(dt, 1H), 7.43(dt, 1H), 7.56(d, 1H), 7.92(dd, 1H) 8.19(s, 1H) 8.41(dd, 1H) 9.08(s, 1H)
3-3		0.36 (*n*-hexane: AcOEt=1:1)	2.23(s, 3H), 2.62(d, 3H), 3.69(s, 3H)4.53-4.44(m, 1H),6.62(dd, 1H),6.69(bs, 1H),7.10(d, 1H),7.19(t, 1H), 7.48(d, 1H),7.51(dd, 1H), 7.93(dd, 1H), 8.22(s, 1H), 8.44(dd, 1H) 9.09(s1, 1H)
3-4		0.41 (*n*-hexane: AcOEt=1:1)	2.32(s, 3H), 2.63(d, 3H), 4.45-4.44(bm, 1H), 6.85(d, 1H), 6.91(d, 1H), 7.00(bs, 1H), 7.28-7.24(m, 1H), 7.57(t, 1H), 7.99(dd, 1H), 8.25 (s, 1H), 8.39(d, 1H),9.00(bs, 1H)
3-5		0.39 (*n*-hexane: AcOEt=1:1)	2.33(s, 3H) 2.63(d, 3H), 3.87(s, 3H), 4.46-4.44(bm, 1H), 6.66(d, 1H),6.71(s, 1H), 7.48(bs, 1H), 7.63-7.59(m, 1H), 7.97(dd, 1H), 8.05(d, 1H), 8.23 (s, 1H), 8.44(d, 1H),8.92(bs, 1H)
3-6		0.27 (*n*-hexane: AcOEt=3:1)	2.63(d, 3H) ,3.90(s, 3H),4.45-4.40(bm, 1H),6.90-6.86.(m, 2H), 7.00-6.96.(m, 1H), 7.23-7.17 (m, 3H), 7.45(t, 1H),64-7.60(m, 2H), 7.97(dd, 1H), 8.22(d, 1H), 8.26 (s, 1H), 8.43(d, 1H),8.94(bs, 1H)

3-7		0.34 (*n*-hexane: AcOEt=3:1)	2.30(s, 3H) ,2.63(d, 3H),4.44-4.43(bm, 1H), 6.68 (bs, 1H), 7.00-6.68(m, 1H),7.23-7.17(m, 2H), 7.46-7.43(m, 1H),7.76(d, 1H), 7.93(dd, 1H),8.22 (s, 1H), 8.40(d, 1H),9.01(bs, 1H)
3-8		0.12 (*n*-hexane: AcOEt=3:1)	2.62(d, 3H) ,2.81(s, 3H), 4.07-3.98(m, 1H)4.52-4.45(bm, 1H), 6.37(bs, 1H),6.77-6.73 (m, 2H), 7.12(t, 1H),7.24-7.20(m, 1H), 7.30-7.27(m, 1H),7.35(t, 1H), 7.88(dd, 1H),8.18 (s, 1H), 8.41(d, 1H),9.19(bs, 1H)
3-9		0.28 (*n*-hexane: AcOEt=3:1)	2.62(d, 3H),3.94(s, 3H)4.49-4.43(bm, 1H), 6.99-6.90 (m, 3H), 7.18-7.23(m, 1H),7.31-7.24(m, 3H), 7.63(bs, 1H),7.93-7.86(m, 1H), 8.28-8.23(m, 1H),8.28 (s, 1H), 8.45(bs, 1H),8.89(bs, 1H)
3-10		0.23 (*n*-hexane: AcOEt=3:1)	0.91(t, 3H) ,1.37 (dd, 2H), 1.64-1.55 (m, 2H),2.64-2.60 (m, 2H),4.45-4.40 (bm, 1H), 6.69 (bs, 1H), 7.23-7.10(m, 1H),7.46-7.38 (m, 1H),7.73 (d 1H), 7.92 (d, 1H),8.21 (s, 1H), 8.38-8.46 (m, 1H),9.09 (bs, 1H)
3-11		0.12 (*n*-hexane: AcOEt=3:1)	2.63 (d, 3H),4.15-4.10 (bm, 1H), 6.58 (bs, 1H), 7.31-7.10(m, 4H),7.53-7.49 (m, 1H),7.71(d 1H), 7.95 (d, 1H), 8.30-8.23 (bm, 1H),8.26 (s, 1H), 8.45 (d, 1H),9.03 (bs, 1H)
3-12		0.4 (*n*-hexane: AcOEt=3:1)	2.09 (dd, 2H), 2.63 (d, 3H) 2.85(t, 2H) ,2.96 (t, 2H), 4.46-4.43 (m, 2H),6.73 (bs, 1H),6.99 (d, 1H), 7.09 (t, 1H), 7.25-7.20(m, 1H),7.52 (t, 1H),7.74 (d 1H), 7.92 (dd, 1H),8.22 (s, 1H), 8.42 (d, 1H),9.02 (bs, 1H)
3-13		0.33 (AcOEt)	2.63 (d, 3H),4.63-4.64 (bm, 1H), 7.11(d, 2H), 7.18(t, 1H), 7.42-7.34(bm, 1H), 7.58-7.55(m, 1H), 7.96(d, 1H), 8.07(s, 1H), 8.19-8.10(bm, 1H), 8.24(s, 1H), 9.15(s, 1H), 11.6-11.4(bm, 1H)

3-14		0.28 (*n*-hexane: AcOEt=3:1)	2.63(d, 3H), 3.88(s, 3H), 3.89(s, 3H), 4.47-4.41(m, 1H), 6.60(d,1H), 6.92 (t,1H), 7.64 (dd, 1H),7.66-7.61(m,1H), 7.89(d, 1H), 7.98(dd, 1H), 8.26(s, 1H), 8.43(d, 1H), 8.95(s, 1H)
3-15		0.30 (n-hexane: AcOEt=3:1)	2.63(d, 3H), 3.66(s, 3H), 3.85(s, 3H), 4.45-4.44(m, 1H), 6.48(dd,1H), 6.79(d,1H), 7.64(dd, 1H), 7.97(dd, 2H), 8.26(s, 1H), 8.44(d, 1H), 8.96(s, 1H)
3-16		0.22 (*n*-hexane: AcOEt=3:1)	2.17(s, 3H), 2.22(s, 3H), 2.64(s, 3H), 2.63(d, 3H), 4.46-4.44(m, 1H), 6.57(bs, 1H), 7.00(s,1H), 7.17(t,1H), 7.44-7.40(m,1H), 7.44(s, 1H), 7.93(dd, 1H), 8.19(s, 1H), 8.43(d, 1H), 9.06(s, 1H)
3-17		0.46 (AcOEt)	2.22(s,3H), 2.63(d, 3H), 3.68(s, 3H), 3.89(s, 3H), 4.52-4.47(m, 1H), 6.51(s,1H), 6.74(s,1H), 7.12(s,1H), 7.16-7.12(m,1H), 7.40(t, 1H), 7.91(dd, 1H), 8.19(s, 1H), 8.42(d, 1H), 9.12(s, 1H)
3-18		0.35 (*n*-hexane: AcOEt=3:1)	1.16(d, 6H),2.25 (s, 3H), 2.62(d, 3H), 2.77(t, 1H), 4.49-4.48(m, 1H), 7.00(s,1H), 7.15(d,1H)7.41-7.37(m,1H), 7.49(d,2H), 7.54(dd, 1H), 7.92(dd, 1H), 8.21(s, 1H), 8.32(d, 1H), 9.02(s, 1H)
3-19		0.23 (*n*-hexane: AcOEt=1:1)	2.63(d, 3H),3.13-3.10 (m, 4H), 3.87(s, 3H), 3.89-3.86(m, 4H), 4.97-4.93(m, 1H), 6.41(dd,1H),6.52(d,1H), 7.24-7.22(m,1H) 7.32(s,1H), 7.57(t,1H), 7.96(dd, 1H), 8.01(d, 1H), 8.14(s, 1H), 8.44(d, 1H), 8.98 (s, 1H)
3-20		0.36 (*n*-hexane: AcOEt=1:1)	2.22(s, 3H), 2.64(d, 3H), 3.00-3.2.97 (m, 4H), 3.76-3.74(m, 4H), 4.54-4.50(m, 1H), 6.64(d,1H),6.66(t, 1H), 7.11(d,1H) 7.18(t,1H), 7.37(d, 1H), 7.46(t, 1H), 7.93(dd, 1H), 8.22(s, 1H), 8.42(d, 1H), 9.09 (s, 1H)

3-21		0.25 (*n*-hexane: AcOEt=3:1)	2.52(d, 3H), 3.90(s, 3H), 4.36-4.32(m, 1H), 6.60(dd, 1H), 6.84(t, 3H), 7.02-6.98(m, 1H), 7.10(t, 1H), 7.31-7.24(m, 1H), 7.38-7.34(m, 1H), 7.72(s, 1H), 7.87(dd, 1H), 8.11(d, 1H), 8.23(s, 1H), 8.26-8.23(m, 1H), 8.83(s, 1H)
3-22		0.27 (AcOEt)	2.33(s, 3H), 2.65(d, 3H), 3.60-3.45(bm, 8H), 4.53-4.49(m, 1H), 6.74(s, 1H), 7.11(d, 1H), 7.22-7.18(m, 1H), 7.58-7.54(m 1H), 7.94(dd, 1H), 8.00(d, 1H), 8.22(s, 1H), 8.37(d, 1H), 9.13(s, 1H)
3-23		0.38 (AcOEt)	1.24-1.08(m, 2H), 1.46-1.32(m, 2H),1.76-1.67(m, 2H), 1.98-1.90(m, 2H), 2.33(s, 3H), 2.64(d, 3H), 3.95-3.90(m, 1H), 4.49-4.47(m, 1H), 5.89-5.80(bm, 1H), 6.66(s, 1H), 7.15(t, 1H), 7.48-7.31(m, 2H), 7.91(dd, 1H), 8.12(s, 1H), 8.23(s, 1H), 8.41(d, 1H), 9.18(s, 1H)
3-24		0.11 (AcOEt)	2.35(s, 3H), 2.71(s, 3H), 3.07-2.73(m, 2H), 3.86-3.31(m, 6H), 6.85(s, 1H), 7.10(d, 1H), 7.24-7.19(m, 1H),7.52-7.48(m, 1H), 7.66-7.59(m, 2H), 7.93(d, 1H), 8.06(s, 1H), 8.27-8.21(m, 1H), 8.23(s, 1H), 9.11(s, 1H)
3-25		0.5 (*n*-hexane: AcOEt=1:1)	2.52(d, 3H), 2.62(s, 3H), 4.36-4.32(m, 1H), 6.74(s, 1H), 6.87(d, 2H), 7.00-6.91(m, 2H), 7.00-6.97(m, 2H), 7.38(dd, 2H), 7.86(dd, 1H), 7.98(s, 1H), 8.23(s, 1H), 8.28(d, 1H), 9.04(s, 1H)
3-26		0.45 (*n*-hexane: AcOEt=1:1)	1.62-1.34(m, 6H), 2.13(s, 3H), 2.56(d, 3H), 3.01-2.87(m, 4H), 4.54-4.38(m, 1H), 6.59(s, 1H), 6.69-6.59(bm, 1H), 7.02(d, 1H), 7.10-7.07(m, 1H), 7.37(t, 1H), 7.84(dd, 1H), 8.15(s, 1H), 8.34(d, 1H), 9.01(s, 1H)

3-27		0.45 (*n*-hexane: AcOEt=1:1)	2.32(s, 3H), 2.58(d, 3H), 3.75(s, 3H),4.37-4.44(m, 1H), 6.77-6.73(m, 1H), 6.89-6.82(m 1H), 6.97-6.91(m, 2H), 6.96(d, 1H), 7.20(dd, 1H), 7.25-7.24(m, 1H), 7.33-7.29(m, 1H),
3-28		0.35 (*n*-hexane: AcOEt=1:1)	2.34(s, 3H), 2.64(d, 3H), 3.81(s, 3H), 4.57-4.50(m, 1H), 6.76(bs, 1H), 6.91-6.84(m, 41H), 7.04(d, 1H), 7.83(dd, 1H), 8.06(d, 1H), 8.19(dd, 1H), 8.23(s, 1H), 9.00(s, 1H)
3-29		0.45 (*n*-hexane: AcOEt=1:1)	1.50(t, 3H), 2.62 (d, 3H)4.17(dd, 2H),4.51-4.44(m, 1H), 6.95-6.89 (m, 2H), 6.94(d, 1H), 7.16 (dd, 1H), 7.31-7.23(m, 5H), 7.67(s, 1H),7.11(dd, 1H), 7.23(d, 2H), 7.65(s, 1H), 7.88(dd, 1H), 8.28-8.23(m, 1H), 8.28(s, 1H), 8.43(s, 1H), 8.89(s, 1H)
3-30		0.45 (*n*-hexane: AcOEt=1:1)	1.49(t, 3H),2.63(d, 3H), 3.85(s, 3H), 4.16(dd, 2H), 4.55-4.48(m, 1H), 6.81(dd, 1H), 6.95-6.91(m, 3H),7.11(dd, 1H), 7.23(d, 2H), 7.65(s, 1H), 7.90-7.88(m, 1H), 8.28-8.26(m, 1H), 8.27(s, 1H), 8.39(s, 1H), 8.90(s, 1H)
3-31		0.29 (*n*-hexane: AcOEt=1:1)	^{1}H-NMR : ($CDCl_3$) 1.83-1.72 (4H, m), 2.63 (3H, d), 2.66-2.62 (2H, m), 2.80 (2H, t), 4.41-4.44 (1H, m), 6.64 (1H, br.s), 6.92 (1H, d), 7.09 (1H, t), 7.18 (1H, t), 7.45 (1H, t), 7.59 (1H, t), 7.92 (1H, d), 8.20 (1H, s), 8.42 (1H, d), 9.08 (1H, br.s).

Example 4: 2-[5-Bromo-2-(subst. phenylamino)-pyrimidin-4-ylamino]-N-propyl-benzene-sulfonamides

These compounds are prepared in analogy to Example 2 using 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-propyl-benzenesulfonamide and the corresponding aniline to give compounds No. 4-1 to 4-31 having the substituent Rx as listed under Example 3 for compounds No. 3-1 to 3-31.

Preparation of 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-propyl-benzenesulfonamide

To a solution of 5-bromo-2,4-dichloropyrimidine (90 µL, 0.70 mmol) and 2-amino-N-propyl-benzenesulfonamide (100 mg, 0.47 mmol), sodium hydride (54.2 mg, 0.56 mmol) in DMSO (1.0 mL) is added and the resulting solution is stirred at 80°C for 3.0 h. The mixture is poured into

water and extracted with ethyl acetate three times. The organic layer is washed with water and then brine, dried over sodium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane : ethyl acetate = 5 : 1) to afford the title compound as a slightly yellow solid.

^{1}H-NMR (δ, ppm) : 0.89 (t, 3H), 1.41 (q, 2H), 3.56 (t, 2H), 4.92 (br.s, 2H), 6.71 (dd, 1H), 6.77 (t, 1H), 7.33 (t, 1H), 7.54 (dd, 1H), 8.79 (s, 1H)

Rf (hexane : ethyl acetate = 1:1): 0.64

Example 5: 2-[5-Trifluoromethyl-2-(subst. phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamides

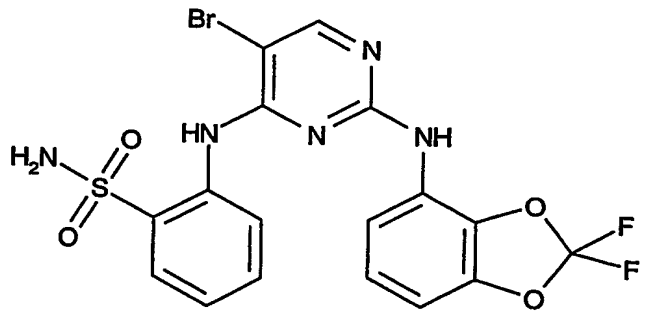
These compounds are prepared in analogy to Example 2 using 2-(2-chloro-5-trifluoromethyl-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide and the corresponding aniline to give compounds No. 5-1 to 5-31 having the substituent Rx as listed under Example 3 for compounds No. 3-1 to 3-31.

Preparation of 2-(2-chloro-5-trifluoromethyl-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide

To a solution of 2,4-dichloro-5-trifluoromethyl-pyrimidine (386 mg, 1.79 mmol) in acetonitrile (10 mL), 2-amino-N-methyl-benzenesulfonamide (333 mg, 1.79 mmol) and 1,8-diaza[5.4.0]-bicyclo-7-undecene (280 µL, 1.88 mmol) are added successively at ambient temperature. After stirring for 15 h at room temperature, dichloromethane (30 mL) is added to the mixture, and the solution is washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride, dried over magnesium sulfate, and evaporated in vacuo. The resulting solid is purified by flash chromatography.

^{1}H NMR ($CDCl_3$) δ: 3.73(s, 3H), 6.67-6.69(m, 1H), 6.72-6.73(m, 1H), 7.27-7.31(m, 1H), 7.78 (dd, 1H), 8.60(s, 1H). Rf (hexane : ethyl acetate = 1:1): 0.28.

Example 6: 2-[5-Bromo-2-(2,3-[difluoromethylenedioxy]phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide



This compound was obtained as a side product formed by N-demethylation on reaction of 2-(5-bromo-2-chloropyrimidin-4-ylamino)-N-methyl-benzenesulfonamide with 2,3-(difluoromethylene-dioxy)aniline following the procedure of Example 2. It may also be prepared by reaction of 2-(5-bromo-2-chloropyrimidin-4-ylamino)benzenesulfonamide with 2,3-(difluoromethylenedioxy)-aniline.

Rf (*n*-hexane: ethyl acetate = 1:1): 0.46.

^{1}H-NMR : ($CDCl_3$) 4.83 (bs, 2H), 6.77 (dd, 1H), 6.86 (s, 1H), 6.97 (t, 1H), 7.31-7.24 (m, 1H), 7.57 (t, 1H), 7.81 (d, 1H), 8.02 (dd, 1H), 8.28 (d, 1H), 8.29 (s, 1H), 8.88 (s, 1H).

Preparation of 2-(5-bromo-2-chloropyrimidin-4-ylamino)benzenesulfonamide: To a solution of 5-bromo-2,4-dichloropyrimidine (300 mg, 1.32mmol) and 2-amino-benzenesulfonamide (340 mg, 1.97 mmol) in 2-propanol (3 mL), concentrated hydrochloric acid (0.06 mL) is added and the mixture is stirred at 90°C for 4.5 hours. The mixture is poured into aqueous sodium hydrogen carbonate and extracted with ethyl acetate three times. The organic layer is washed with water, dried over sodium sulfate, and evaporated in vacuo. The residue is purified by column chromatography (hexane : ethyl acetate = 2:1) to afford the title compound.

Rf (hexane : ethyl acetate = 1:1): 0.55. ^{1}H-NMR (400MHz, CDCl3) δ : 4.78 (br.s, 2H), 7.22 (dd, 1H), 7.61 (ddd, 1H), 7.95 (dd, 1H), 8.35 (s, 1H), 8.35 (d, 1H), 9.18 (s, 1H)

Example 7: Synthesis of substituted amines which are commercially not available:

Preparation of 3-amino-4'-methoxy-4-methylbiphenyl

To a solution of 4-methoxyphenyl-boronic acid (500 mg, 3.29 mmol) in toluene (5.2 mL) and ethanol (1.3 mL), potassium carbonate (910 mg, 6.58 mmol), tetrakis(triphenylphosphine)-palladium (228.1 mg, 0.099 mmol) and 4-bromo-1-methyl-2-nitrobenzene (711 mg, 3.29 mmol) are added and stirred at 100°C for 7 hours. The mixture is poured into water and extracted with ethyl acetate two times. The organic layer is washed with water and then brine, dried over

magnesium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane : ethyl acetate = 5 : 1) to afford the 4'-methoxy-4-methyl-3-nitro-biphenyl as a yellow solid.

^{1}H-NMR (δ, ppm) : 2.62 (s, 3H), 3.86 (s, 3H), 7.02-6.98 (m, 2H), 7.37 (d, 1H), 7.54 (dd, 2H), 7.68 (dd, 1H), 8.18 (d, 1H). Rf (hexane : ethyl acetate = 3:1): 0.40.

A suspension of 4'-methoxy-4-methyl-3-nitrobiphenyl (630 mg, 2.95 mmol) and 10% palladium on charcoal (63 mg, 0.059 mmol) in methanol (6 mL) is stirred under hydrogen atmosphere for 12 hours. Palladium catalyst is removed by filtration and the resulting solution is evaporated in vacuo to afford the title compound.

^{1}H-NMR (δ, ppm) : 2.20 (s, 3H), 3.84 (s, 3H), 6.87 (d, 1H), 6.89 (dd, 1H), 6.95 (d, 2H), 7.09 (d, 1H), 7.48 (d, 2H). Rf (n-hexane : ethyl acetate = 1:1): 0.50.

Preparation of 4-(3-amino-4-methylbenzoyl)-piperazine-1-carboxylic acid tert-butyl ester

To a solution of 4-methyl-3-nitro-benzoic acid (300 mg, 2.76 mmol), N-butoxycarbonyl-piperazine (340 mg, 1.83 mmol) in DMF (3.0 mL), triethylamine (300 μL, 3.59 mmol), TBTU (800 mg, 2.49 mmol) and HOAt (270.5 mg,1.99 mmol) are added and stirred at room temperature for 24 hours. The mixture is poured into water and extracted twice with ethyl acetate. The organic layer is washed with water and then brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane : ethyl acetate = 5 : 1) to afford 4-(4-methyl-3-nitrobenzoyl)-piperazine-1-carboxylic acid tert-butyl ester as a colorless solid.

^{1}H-NMR (δ, ppm) : 1.47 (s, 9H), 2.64 (s, 3H), 3.28-3.88 (bm, 8H), 7.42 (d, 1H), 7.56 (dd, 1H), 8.03 (d, 1H). Rf (hexane : ethyl acetate = 10:1): 0.13.

The title compound is obtained by reduction with hydrogen over 10% palladium on charcoal in methanol solution.

Preparation of 4-(3-amino-4-methylphenyl)-morpholine

To a solution of 4-bromo-1-methyl-2-nitrobenzene (225 mg, 1.04 mmol), morpholine (125 μL, 1.25 mmol), and cesium carbonate (474.4 mg, 1.46 mmol) in toluene, palladium diacetate (31.2 mg, 0.139 mmol) and 2-(di-t-butylphosphino)biphenyl (125 mg, 0.403 mmol) are added and stirred at 100°C for 5 hours. After cooling, the mixture is filtered to remove insoluble material. The filtrate is poured into water and extracted with ethyl acetate twice. The organic layer is washed with water and then brine, dried over magnesium sulfate, and evaporated in vacuo. The

residue is purified with silica gel column chromatography (n-hexane : ethyl acetate = 5 : 1) to afford 4-(4-methyl-3-nitrophenyl)-morpholine as a yellow solid.
^{1}H-NMR (δ, ppm) : 2.50 (s, 3H), 3.17-3.19 (m, 4H), 3.86-3.88(m, 4H), 7.04 (dd, 1H), 7.21 (d, 1H), 7.47 (d, 1H). Rf (hexane : ethyl acetate = 5:1): 0.20.
The title compound is obtained by reduction with hydrogen over 10% palladium on charcoal in methanol solution.

Example 8: Sulfonamide moieties are prepared as follows:
Preparation of 2-amino-4-chloro-5-methyl-benzenesulfonyl chloride
To a solution of 2-amino-5-chloro-4-methyl-benzenesulfonic acid (3.0 g, 1.35 mmol) in dichloroethane (10 mL) is added sulfuryl chloride (4.4 mL, 3.83 mmol) and stirred at 60°C. After one hour, thionyl chloride (1.3 mL) is added and the mixture is further stirred at 100°C for 7.0 hours. The mixture is poured into iced water and extracted with ether three times. The organic layer is washed with water and then brine, dried over sodium sulfate, and evaporated in vacuo.
^{1}H-NMR (δ, ppm) : 2.35 (s, 3H), 6.68 (s, 1H), 7.75 (s, 1H).
This substituted sulfonyl chloride is reacted with a suitable amine. On reaction e.g. with methylamine, 2-amino-5-chloro-4,N-dimethylbenzenesulfonamide is formed.

Example 9: FAK Assay
All steps are performed in a 96-well black microtiter plate. Purified recombinant hexahistidine-tagged human FAK kinase domain is diluted with dilution buffer (50 mM HEPES, pH 7.5, 0.01% BSA, 0.05% Tween-20 in water) to a concentration of 94 ng/mL (2.5 nM). The reaction mixture is prepared by mixing 10 µL 5x kinase buffer (250 mM HEPES, pH 7.5, 50 µM Na_3VO_4, 5 mM DTT, 10 mM $MgCl_2$, 50 mM $MnCl_2$, 0.05% BSA, 0.25% Tween-20 in water), 20 µL water, 5 µL of 4 µM biotinylated peptide substrate (Biot-Y397) in aqueous solution, 5 µL of test compound in DMSO, and 5 µL of recombinant enzyme solution and incubated for 30 min at room temperature. The enzyme reaction is started by addition of 5 µL of 5 µM ATP in water and the mixture is incubated for 3 hours at 37°C. The reaction is terminated by addition of 200 µL of detection mixture (1 nM Eu-PT66, 2.5 µg/mL SA-(SL)APC, 6.25 mM EDTA in dilution buffer), and the FRET signal from europium to allophycocyanin is measured by ARVOsx+L (Perkin Elmer) after 30 min of incubation at room temperature. The ratio of fluorescence intensity of 665 nm to 615 nm is used as a FRET signal for data analysis in order to cancel the colour quenching effect by a test compound. The results are shown as percent inhibition of enzyme activity. DMSO and 0.5 M EDTA are used as a control of 0% and 100% inhibition, respectively.

IC50 values are determined by non-linear curve fit analysis using the OriginPro 6.1 program (OriginLab).

The Biot-Y397 peptide (Biotin-SETDDYAEIID ammonium salt) is designed to have the same amino acid sequence as the region from S392 to D402 of human (GenBank Accession Number L13616) and is prepared by standard methods.

Purified recombinant hexahistidine-tagged human FAK kinase domain is obtained in the following way: Full-length human FAK cDNA is isolated by PCR amplification from human placenta Marathon-Ready™ cDNA (Clontech, No. 7411-1) with the 5' PCR primer (ATGGCAGCTGCTTACCTTGAC) and the 3' PCR primer (TCAGTGTGGTCTCGTCTGCCC) and subcloned into a pGEM-T vector (Promega, No. A3600). After digestion with AccIII, the purified DNA fragment is treated with Klenow fragment. The cDNA fragment is digested with BamHI and cloned into pFastBacHTb plasmid (Invitrogen Japan K.K., Tokyo) previously cut with BamHI and Stu I. The resultant plasmid, hFAK KD (M384-G706)/pFastBacHTb, is sequenced to confirm its structure. The resulting DNA encodes a 364 amino acid protein containing a hexahistidine tag, a spacer region and a rTEV protease cleavage site at the N-terminal and the kinase domain of FAK (Met384-Gly706) from position 29 to 351.

Donor plasmid is transposed into the baculovirus genome, using MaxEfficacy DH10Bac *E.coli* cells. Bacmid DNA is prepared by a simple alkaline lysis protocol described in the Bac-to-Bac® Baculovirus Expression system (Invitrogen). Sf9 insect cells are transfected based on the protocol provided by the vendor (CellFECTIN®, Invitrogen). The expression of FAK in each lysate is analysed by SDS-PAGE and Western blotting with anti-human FAK monoclonal antibody (clone #77 from Transduction Laboratories).

The virus clone that shows the highest expression is further amplified by infection to Sf9 cells. Expression in ExpresSF+® cells (Protein Sciences Corp., Meriden, Connecticut, USA) gives high level of protein with little degradation. Cell lysates are loaded onto a column of HiTrap™ Chelating Sepharose HP (Amersham Biosciences) charged with nickel sulfate and equilibrated with 50 mM HEPES pH 7.5, 0.5 M NaCl and 10 mM imidazole. Captured protein is eluted with increasing amounts of imidazole in HEPES buffer / NaCl, and further purified by dialysis in 50 mM HEPES pH 7.5, 10% glycerol and 1 mM DTT.

Example 10: Cell-free ZAP-70 Kinase assay

The ZAP-70 kinase assay is based on time-resolved fluorescence resonance energy transfer (FRET). 80 nM ZAP-70 are incubated with 80 nM Lck (lymphoid T-cell protein tyrosine kinase) and 4 μM ATP in ZAP-70 kinase buffer (20 mM Tris, pH 7.5, 10 μM Na_3VO_4, 1 mM DTT, 1 mM $MnCl_2$, 0.01 % BSA, 0.05 % Tween-20) for 1 hour at room temperature in a siliconized polypropylene tube. Then, the selective Lck inhibitor PP2 (1-tert-butyl-3-(4-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamine; Alexis Biochemicals) is added (final concentration 1.2 μM) and incubated for further 10 min. 10 μL of this solution is mixed with the 10 μL biotinylated peptide LAT-11 (1 μM) as substrate and 20 μL of serial dilutions of inhibitors and incubated for 4 hours at room temperature. The kinase reaction is terminated with 10 μL of a 10 mM EDTA solution in detection buffer (20 mM Tris, pH 7.5, 0.01 % BSA, 0.05 % Tween-20). 50 μL europium-labelled anti-phosphotyrosine antibody (Eu-PT66; final concentration 0.125 nM); and 50 μL streptavidin-allophycocyanine (SA-APC; final concentration 40 nM) in detection buffer are added. After 1 hour incubation at room temperature fluorescence is measured on the Victor2 Multilabel Counter (Wallac) at 665 nm. Background values (low control) are obtained in the absence of test samples and ATP and are subtracted from all values. Signals obtained in the absence of test samples are taken as 100% (high control). The inhibition obtained in the presence of test compounds is calculated as percent inhibition of the high control. The concentration of test compounds resulting in 50% inhibition (IC_{50}) is determined from the dose-response curves. In this assay, the agents of the invention have IC_{50} values in the range of 10 nM to 2 μM, preferably from 10 nM to 100 nM.

Recombinant ZAP-70 kinase is obtained as follows: A nucleic acid encoding full-length human ZAP-70 (GenBank #L05148) is amplified from a Jurkat cDNA library by RT-PCR and cloned into the pBluescript KS vector (Stratagene, California, USA). The authenticity of the ZAP-70 cDNA insert is validated by complete sequence analysis. This donor plasmid is then used to construct a recombinant baculovirus transfer vector based on the plasmid pVL1392 (Pharmingen, California, USA) featuring in addition an N-terminal hexahistidine tag. Following co-transfection with AcNPV viral DNA, 10 independent viral isolates are derived via plaque-purification, amplified on small scale and subsequently analyzed for recombinant ZAP-70 expression by Western Blot using a commercially available anti-ZAP-70 antibody (Clone 2F3.1, Upstate Biotechnology, Lake Placid, NY, USA). Upon further amplification of one positive recombinant plaque, titrated virus stocks are prepared and used for infection of Sf9 cells grown in serum-free SF900 II medium (Life Technologies, Basel, Switzerland) under defined, optimized conditions.

ZAP-70 protein is isolated from the lysate of infected Sf9 cells by affinity chromatography on a Ni-NTAcolumn (Qiagen, Basel, Switzerland).
Recombinant His-tagged ZAP-70 is also available from PanVera LLC, Madison, Wisconsin, USA.

LAT-11 (linker for activation of T cell): The biotinylated peptide LAT-11 (Biotin-EEGAPDYENLQELN) used as a substrate in the ZAP-70 kinase assay is prepared in analogy to known methods of peptide synthesis. The N-α Fmoc group of Fmoc-Asn(Trt)-oxymethyl-4-phenoxymethyl-co(polystyrene-1%-divinyl-benzene), content of Asn approx. 0.5 mmol/g, is cleaved using piperidine, 20% in DMF. Four equivalents per amino-group of Fmoc-amino acid protected in their side chains [Asp(OtBu), Glu(OtBu), Asn(Trt), Gln(Trt) and Tyr(tBu)] are coupled using DIPCDI and HOBt in DMF. After complete assembly of the peptide chain the terminal Fmoc-protecting group is removed with piperidine in DMF as before. L(+)-biotinyl-aminohexanoic acid is then coupled to the terminal amino group using DIPCDI and HOBt in DMF using four equivalents of the reagents for four days at RT. The peptide is cleaved from the resin support and all side-chain protecting groups are simultaneously removed by using a reagent consisting of 5% dodecylmethylsulfide and 5% water in TFA for two hours at RT. Resin particles are filtered off, washed with TFA and the product is precipitated from the combined filtrates by the addition of 10 to 20 volumes of diethyl ether, washed with ether and dried. The product is purified by chromatography on a C-18 wide-pore silica column using a gradient of acetonitrile in 2% aqueous phosphoric acid. Fractions containing the pure compound are collected, filtered through an anion-exchange resin (Biorad, AG4-X4 acetate form) and lyophilized to give the title compound. MS: 1958.0 $(M-H)^{-1}$

Example 11: Phosphorylation levels of FAK

Phosphorylation levels of FAK at Tyr397 was quantified by the sandwich ELISA. Mouse mammary carcinoma 4T1 cells (1×10^5) were plated in wells of 96-well culture plates and incubated with or without various concentrations of inhibitors for 1 h in Dulbecco's modified eagle medium containing 0.5% BSA. The medium was removed and cells were lysed in 200 µL 50 mM Tris-HCl, pH 7.4, containing 1% NP-40, 0.25% sodium deoxycholate, 150 mM NaCl, 1 mM EDTA, 1 mM PMSF, 1 mM Na_3VO_4, 1 mM NaF, 1 µg/mL aprotinin, 1 µg/mL leupeptin and 1 µg/mL pepstatin. After centrifugation, the supernatants were subjected to a sandwich ELISA to quantify the phosphorylated FAK and total FAK. Cell lysates were applied to 96-well flat-bottom ELISA plates which had been pre-coated with 100 µL/well of 4 µg/mL mouse monoclonal anti-

FAK antibody (clone 77, Becton Dickinson Transduction Laboratories) in 50 mM Tris-HCl, pH 9.5, containing 150 mM NaCl for 18 h at 4°C and blocked with 300 μL of BlockAce (Dainippon Pharmaceuticals Co.) diluted at 1:4 with H_2O at room temperature for 2 h. After washing with TBSN (20 mM Tris-HCl, pH 8.3, containing 300 mM NaCl, 0.1% SDS and 0.05% NP-40), total FAK was detected with 100 μL of 1 μg/ml anti-FAK polyclonal antibody (#65-6140, Upstate Biology Inc.), and phosphorylated FAK was detected with 100 μL of 0.25 μg/μL anti-phosphorylated FAK (Y397) antibody (Affinity BioReagents, #OPA1-03071) in BlockAce diluted at 1:10 with H_2O. After 1 h incubation at room temperature, plates were washed with TBSN and 100 μL of biotinylated anti-rabbit IgG (#65-6140, Zymed Laboratolies Inc.) diluted at 1:2000 with BlockAce diluted at 1:10 with H_2O was incubated at room temperature for 1 h. After washing with TBSN, ABTS solution substrate kit (#00-2011, Zymed Lobolatories Inc.) was used for color development. Absorbance at 405 nm was measured after 20 min incubation at room temparature. The concentration of compound causing 50% reduction of phosphorylation level of FAK was determined.

Example 12: Anchorage-independent tumor cell growth assay

Mouse mammary carcinoma 4T1 cells (5×10^3) were plated in 96-well Ultra low Attachment plates (#3474, Corning Inc.) in 100 μL of Dulbecco's modified eagle medium containing 10% FBS. Cells were cultured for 2 h and inhibitors were added at various concentrations in a final concentration of 0.1% DMSO. After 48 h, cell growth was assayed with the cell counting kit-8 (Wako Pure Chemical), which uses a water soluble tetrazolium salt WST8. Twenty μL of the reagent was added into each well and cells were further cultured for 2 h. The optical density was measured at 450 nm. The concentration of compound causing 50 % inhibition of growth was determined.

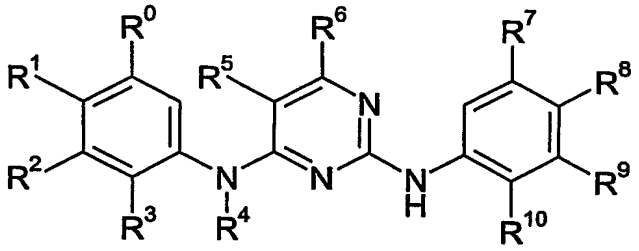
Table

The following test results were obtained using the methods described in Examples 9, 11 and 12:

Compound	FAK IC_{50} (nM)	phospho-FAK ELISA IC_{50} (mM)	4T1 cell growth IC_{50} (mM)
	Example 9	Example 11	Example 12
No. 1	140	0.7	>10
No. 3-1	44(37)	0.34	>10
No. 3-2	36	0.85	4
No. 3-3	9.1	0.14 (0.17)	0.5, 0.8 (2)
No. 3-4	32	0.53	2
No. 3-5	21(18)	0.07, 0.17 (0.1)	2, 1 (2)
No. 3-6	13	0.11	2
No. 3-7	16	0.45	2
No. 3-8	74	0.3	6
No. 3-9	48,24(16)	0.36, 0.5 (0.3)	0.7, 0.7 (2)
No. 3-10	52	0.95	>10
No. 3-11	9(8)	0.04, 0.02 (0.009)	0.3 (0.3)
No. 3-12	5.4	0.006	1
No. 3-13	58(49)	1.7, 0.5 (0.7)	0.6, 0.3 (3)
No. 3-14	54	0.4	5
No. 3-15	7	0.02, 0.02 (0.026)	0.8, 0.6 (1)
No. 3-16	48	1.1	3
No. 3-17	2.8	0.03, 0.02 (0.019)	0.1, 0.2 (0.3)
No. 3-18	130	1.5	9
No. 3-19	6.8	0.2, 0.35 (0.01)	0.3, 0.8 (0.2)
No. 3-20	16	0.22	0.3
No. 3-21	[22]	3	>10
No. 3-22	120	0.9	2
No. 3-23	38	0.39	0.5
No. 3-24	64	3.5	5
No. 3-25	22	0.3, 0.23 (0.25)	0.2, 0.3 (0.2)
No. 3-26	50	0.79	2
No. 3-28	43	0.71	0.7
No. 3-29	89	0.6	>10
No. 3-30	69	0.6	3
No. 3-31	13	1.1	5

Claims

1. A compound of formula I



(I)

wherein

each of R^0, R^1, R^2,and R^3 independently is hydrogen, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkinyl, C_3-C_8cycloalkyl, C_3-C_8cycloalkylC_1-C_8alkyl, C_5-C_{10}arylC_1-C_8alkyl, hydroxyC_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl, aminoC_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1, 2 or 3 hetero atoms selected from N, O and S, hydroxy, C_1-C_8alkoxy, hydroxyC_1-C_8alkoxy, C_1-C_8alkoxyC_1-C_8alkoxy, haloC_1-C_8alkoxy, unsubstituted or substituted C_5-C_{10}arylC_1-C_8alkoxy, unsubstituted or substituted heterocyclyloxy, or unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstitued or substituted amino, C_1-C_8alkylthio, C_1-C_8alkylsulfinyl, C_1-C_8alkylsulfonyl, C_5-C_{10}arylsulfonyl, halogen, carboxy, C_1-C_8alkoxycarbonyl, unsubstitued or substituted carbamoyl, unsubstitued or substituted sulfamoyl, cyano or nitro; or

R^0 and R^1, R^1 and R^2, and/or R^2 and R^3 form, together with the carbon atoms to which they are attached, a 5 or 6 membered carbocyclic or heterocyclic ring comprising 0, 1, 2 or 3 heteroatoms selected from N, O and S;

R^4 is hydrogen or C_1-C_8alkyl;

each of R^5 and R^6 independently is hydrogen, C_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl, haloC_1-C_8alkyl, C_1-C_8alkoxy, halogen, carboxy, C_1-C_8alkoxycarbonyl, unsubstitued or substituted carbamoyl, cyano, or nitro; and

each of R^7, R^8, R^9, and R^{10} independently is C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkinyl, C_3-C_8cycloalkyl, C_3-C_8cycloalkylC_1-C_8alkyl, C_5-C_{10}arylC_1-C_8alkyl, hydroxyC_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl, aminoC_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1, 2 or 3 hetero atoms selected from N, O and S, hydroxy, C_1-C_8alkoxy, hydroxyC_1-C_8alkoxy, C_1-C_8alkoxyC_1-C_8alkoxy, haloC_1-C_8alkoxy, unsubstituted or substituted C_5-C_{10}arylC_1-C_8alkoxy, unsubstituted or substituted heterocyclyloxy, or unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstitued or substituted amino, C_1-C_8alkylthio, C_1-C_8alkylsulfinyl, C_1-

C_8alkylsulfonyl, C_5-C_{10}arylsulfonyl, halogen, carboxy, C_1-C_8alkoxycarbonyl, unsubstitued or substituted carbamoyl, unsubstitued or substituted sulfamoyl, cyano or nitro;

or each of R^7, R^8 and R^9 independently is hydrogen;

or R^7 and R^8, R^8 and R^9, and/or R^9 and R^{10} form together with the carbon atoms to which they are attached, a 5 or 6 membered carbocyclic or heterocyclic ring comprising 0, 1, 2 or 3 heteroatoms selected from N, O and S;

and salts thereof.

2. A compound of formula I according to claim 1, wherein

each of R^0 or R^2 independently is hydrogen, C_1-C_8alkyl, hydroxyC_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1-C_8alkoxy, haloC_1-C_8alkoxy, C_5-C_{10}aryloxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, C_1-C_8alkylsulfonyl, halogen, unsubstituted or substituted carbamoyl, unsubstituted or substituted sulfamoyl;

R^1 is hydrogen, C_1-C_8alkyl, hydroxyC_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1-C_8alkoxy, haloC_1-C_8alkoxy, C_5-C_{10}aryloxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, C_1-C_8alkylsulfonyl, halogen, unsubstituted or substituted carbamoyl, unsubstituted or substituted sulfamoyl;

R^3 is hydrogen, C_1-C_8alkyl, hydroxyC_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 heteroatoms selected from N, O and S, C_1-C_8alkoxy, substituted amino, C_1-C_8alkylsulfonyl, C_5-C_{10}arylsulfonyl, halogen, carboxy, substituted or unsubstituted carbamoyl, unsubstituted or substituted sulfamoyl; or

each pair of adjacent substituents R^0 and R^1, or R^1 and R^2, or R^2 and R^3 is -CH_2-NH-CO-, -CH_2-CH_2-NH-CO-, -CH_2-CO-NH-, -CH_2-CH_2-CO-NH-, -CH_2-NH-SO_2-, -CH_2-CH_2-NH-SO_2-, -CH_2-SO_2-NH-, -CH_2-CH_2-SO_2-NH-, -CH_2-CH_2-SO_2-, -CH_2-CH_2-CH_2-SO_2-, -O-CH_2-O-, or -O-CF_2-O-, and such pairs wherein hydrogen in NH is replaced by C_1-C_8alkyl;

R^4 is hydrogen or C_1-C_8alkyl;

R^5 is hydrogen; C_1-C_8alkyl, halogen, haloC_1-C_8alkyl, cyano or nitro;

R^6 is hydrogen;

each of R^7 and R^9 independently is hydrogen, C_1-C_8alkyl, hydroxyC_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1-C_8alkoxy, haloC_1-C_8alkoxy, C_5-C_{10}aryloxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, C_1-C_8alkylsulfonyl, halogen, unsubstituted or substituted carbamoyl, unsubstituted or substituted sulfamoyl;

R^8 is hydrogen, C_1-C_8alkyl, hydroxyC_1-C_8alkyl, haloC_1-C_8alkyl, C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1-C_8alkoxy, haloC_1-C_8alkoxy, C_5-C_{10}aryloxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, C_1-C_8alkylsulfonyl, halogen, unsubstituted or substituted carbamoyl, unsubstituted or substituted sulfamoyl, cyano, or nitro; and

R^{10} is C_1-C_8alkyl, hydroxyC_1-C_8alkyl, haloC_1-C_8alkyl, C_1-C_8alkoxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, halogen, carboxy, carbamoyl, or unsubstituted or substituted sulfamoyl; or

each pair of adjacent substituents R^7 and R^8, or R^8 and R^9 or R^9 and R^{10}, is –NH-CH=CH-, -CH=CH-NH-, –NH-N=CH-, –CH=N-NH-, -CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2-, -CH_2-CH_2-O-, -CH=CH-O-, -O-CH_2-O-, or -O-CF_2-O-.

3. A compound of formula I according to claim 1, wherein

each of R^0 or R^2 independently is hydrogen, C_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1-C_8alkoxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, or halogen;

R^1 is hydrogen, C_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1-C_8alkoxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, halogen;

R^3 is hydrogen, C_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 heteroatoms selected from N, O and S, C_1-C_8alkoxy, substituted amino, C_1-C_8alkylsulfonyl, C_5-C_{10}arylsulfonyl, halogen, carboxy, substituted or unsubstituted carbamoyl, or unsubstituted or substituted sulfamoyl; or

each pair of adjacent substituents R^0 and R^1, or R^1 and R^2, or R^2 and R^3 is $-CH_2-NH-CO-$, $-CH_2-NH-SO_2-$, $-CH_2-CH_2-SO_2-$, $-O-CH_2-O-$, or $-O-CF_2-O-$, and such pairs wherein hydrogen in NH is replaced by C_1-C_8alkyl;

R^4 is hydrogen;

R^5 is hydrogen, halogen, haloC_1-C_8alkyl, or nitro;

R^6 is hydrogen;

each of R^7 and R^9 independently is hydrogen, C_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1-C_8alkoxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, halogen, unsubstituted or substituted carbamoyl, or unsubstituted or substituted sulfamoyl;

R^8 is hydrogen, C_1-C_8alkyl, haloC_1-C_8alkyl, C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1-C_8alkoxy, haloC_1-C_8alkoxy, C_5-C_{10}aryloxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, halogen, unsubstituted or substituted sulfamoyl, or nitro; and

R^{10} is C_1-C_8alkyl, haloC_1-C_8alkyl, C_1-C_8alkoxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, or halogen; or

each pair of adjacent substituents R^7 and R^8, or R^8 and R^9 or R^9 and R^{10}, is –NH-CH=CH-, -CH=CH-NH-, –NH-N=CH-, –CH=N-NH-, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-O-CH_2-O-$, or $-O-CF_2-O-$.

4. A compound of formula I according to claim 1, wherein

each of R^0 or R^2 independently is hydrogen, piperazino, N-methylpiperazino or 1-methyl-4-piperidyloxy;

R^1 is hydrogen, piperazino, N-methylpiperazino, morpholino, 1-methyl-4-piperidinyloxy, 3-morpholinopropoxy or 2-morpholinoethoxy;

R^3 is sulfamoyl, methylsulfamoyl or propylsulfamoyl; or

the pair of adjacent substituents R^0 and R^1, or R^1 and R^2 is $-O-CH_2-O-$, or the pair of adjacent substituents R^2 and R^3 is $-CH_2-NH-CO-$ or $-CH_2-NH-SO_2-$;

R^4 is hydrogen;

R^5 is hydrogen, chloro, bromo, trifluoromethyl or nitro;

R^6 is hydrogen;

each of R^7 and R^9 independently is hydrogen, C_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1-C_8alkoxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, halogen, unsubstituted or substituted carbamoyl, or unsubstituted or substituted sulfamoyl;

R^8 is hydrogen, C_1-C_8alkyl, haloC_1-C_8alkyl, C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1-C_8alkoxy, haloC_1-C_8alkoxy, C_5-C_{10}aryloxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, halogen, unsubstituted or substituted sulfamoyl, or nitro; and

R^{10} is C_1-C_8alkyl, haloC_1-C_8alkyl, C_1-C_8alkoxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, or halogen; or

each pair of adjacent substituents R^7 and R^8, or R^8 and R^9 or R^9 and R^{10}, is –NH-CH=CH-, -CH=CH-NH-, –NH-N=CH-, –CH=N-NH-, -CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2-, -O-CH_2-O-, or -O-CF_2-O-.

5. A compound of formula I according to claim 1, wherein

each of R^0 or R^2 independently is hydrogen, piperazino, N-methylpiperazino or 1-methyl-4-piperidyloxy;

R^1 is hydrogen, piperazino, N-methylpiperazino, morpholino, 1-methyl-4-piperidinyloxy, 3-morpholinopropoxy or 2-morpholinoethoxy;

R^3 is sulfamoyl, methylsulfamoyl or propylsulfamoyl; or

the pair of adjacent substituents R^0 and R^1, or R^1 and R^2 is -O-CH_2-O-, or the pair of adjacent substituents R^2 and R^3 is -CH_2-NH-CO- or -CH_2-NH-SO_2-;

R^4 is hydrogen;

R^5 is hydrogen, chloro, bromo, trifluoromethyl or nitro;

R^6 is hydrogen;

each of R^7 and R^9 independently is hydrogen, methyl, isopropyl, trifluoromethyl, phenyl, o-, m- or p-methoxyphenyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, isopropoxy, phenoxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 2-(1-imidazolyl)ethoxy, dimethylamino, fluoro, morpholinocarbonyl, piperidinocarbonyl, piperazinocarbonyl or cyclohexylcarbamoyl;

R^8 is hydrogen, methyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, trifluoromethoxy, phenoxy, 1-methyl-4-piperidyloxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 3-(N-methylpiperazino)-propoxy, methylamino, fluoro, chloro, sulfamoyl or nitro; and

R^{10} is methyl, butyl, methoxy, ethoxy, 2-(1-imidazolyl)ethoxy, methylamino, dimethylamino or fluoro; or

the pair of adjacent substituents R^7 and R^8 or R^8 and R^9 is $-O-CH_2-O-$ or the pair of adjacent substituents R^9 and R^{10} is -NH-CH=CH-, -CH=N-NH-, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$ or $-O-CF_2-O-$.

6. A compound of formula I according to claim 1, wherein

each of R^0, R^1 or R^2 is hydrogen;

R^3 is sulfamoyl, methylsulfamoyl or propylsulfamoyl;

R^4 is hydrogen;

R^5 is chloro or bromo;

R^6 is hydrogen;

each of R^7 and R^9 independently is hydrogen, methyl, isopropyl, trifluoromethyl, phenyl, o-, m- or p-methoxyphenyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, isopropoxy, phenoxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 2-(1-imidazolyl)ethoxy, dimethylamino, fluoro, morpholinocarbonyl, piperidinocarbonyl, piperazinocarbonyl or cyclohexylcarbamoyl;

R^8 is hydrogen, methyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, trifluoromethoxy, phenoxy, 1-methyl-4-piperidyloxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 3-(N-methylpiperazino)-propoxy, methylamino, fluoro, chloro, sulfamoyl or nitro; and

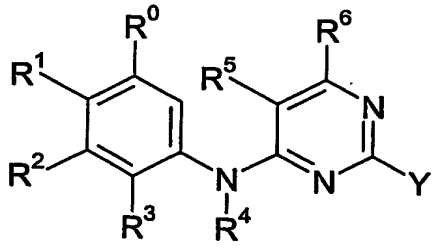
R^{10} is methyl, butyl, methoxy, ethoxy, 2-(1-imidazolyl)ethoxy, methylamino, dimethylamino or fluoro; or

the pair of adjacent substituents R^7 and R^8 or R^8 and R^9 is $-O-CH_2-O-$, or the pair of adjacent substituents R^9 and R^{10} is -NH-CH=CH-, -CH=N-NH-, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$ or $-O-CF_2-O-$.

7. The compound of formula I according to claim 1, wherein each of R^0, R^1 or R^2 is hydrogen, R^3 is methylsulfamoyl, R^4 is hydrogen, R^5 is bromo, R^6 is hydrogen, each of R^7 and R^8 is methoxy, R^9 is hydrogen, and R^{10} is methyl.

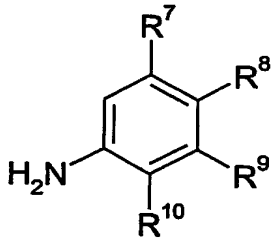
8. The compound of formula I according to claim 1, wherein each of R^0, R^1 or R^2 is hydrogen, R^3 is methylsulfamoyl, R^4 is hydrogen, R^5 is bromo, R^6 is hydrogen, each of R^7 and R^8 is hydrogen, and the pair of adjacent substituents R^9 and R^{10} is $-CH_2-CH_2-CH_2-$.

9. A process for the production of a compound of formula I according to claim 1, comprising reacting a compound of formula II



(II)

wherein R^0, R^1, R^2, R^3, R^4, R^5, and R^6 are as defined in claim 1, and Y is a leaving group, with a compound of formula III



(III)

wherein R^7, R^8, R^9 and R^{10} are as defined in claim 1;

and, if desired, converting a compound of formula I, wherein the substituents have the meaning as defined in claim 1, into another compound of formula I as defined in claim 1;

and recovering the resulting compound of formula I in free from or as a salt, and, when required, converting the compound of formula I obtained in free form into the desired salt, or an obtained salt into the free form.

10. A pharmaceutical composition comprising a compound of formula I, wherein the substituents have the meaning as defined in claim 1, as active ingredient together with one or more pharmaceutically acceptable diluents or carriers.

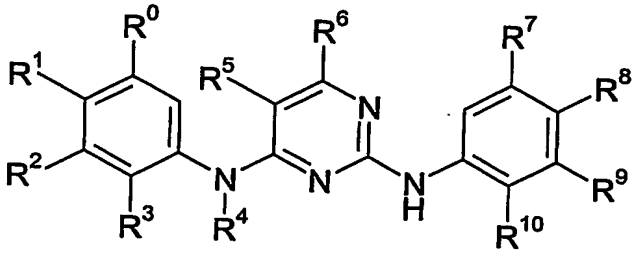
11. The use of a compound of formula I, wherein the substituents have the meaning as defined in claim 1, for the manufacture of a medicament for the treatment or prevention of neoplastic diseases and immune system disorders.

12. A combination comprising a therapeutically effective amount a compound of formula I, wherein the substituents have the meaning as defined in claim 1, and one or more further drug substances, said further drug substance being useful in the treatment of neoplastic diseases or immune system disorders.

13. A method for the treatment of neoplastic diseases and immune system disorders in a subject in need thereof which comprises administering an effective amount of a compound of formula I, wherein the substituents have the meaning as defined in claim 1, or a pharmaceutical composition comprising same.

Abstract

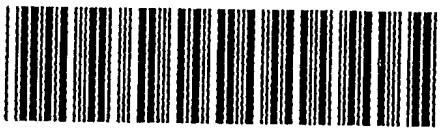
Compounds of formula I



(I)

wherein the substituents R^0 to R^{10} are as defined in the specification, are inhibitors of Focal Adhesion Kinase (FAK), a key enzyme in the integrin-mediated outside-in signal cascade. The compounds are thus indicated for the treatment of neoplastic diseases and immune system disorders.

PCT/EP2004/002616



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